REVIEW ARTICLE

MEDICAL PROGRESS

Advances in Malignant Mesothelioma

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Malignant mesothelioma is an aggressive tumor of serosal surfaces, such as the pleura and the peritoneum.[1] This tumor was once rare, but its incidence is increasing worldwide, probably as a result of widespread exposure to asbestos, a factor with which it is associated (Table 1).[8] There is substantial interest in this disease on the part of the medical community and the general public, because millions of people have been exposed to asbestos fibers, and many articles about the dangers of asbestos have appeared in the press.

In addition to its substantial personal and health care costs, malignant mesothelioma is associated with compensation costs that are a considerable problem for industry and government. The predicted total economic burden of malignant mesothelioma related to compensation for asbestos exposure in the next 40 years is up to $200 billion for the United States[9] and $80 billion for Europe.[6]

In this article we review the key advances in the understanding, diagnosis, and management of malignant mesothelioma that have occurred in the past 5 to 10 years.

Clinical Features

Eighty percent of patients with pleural malignant mesothelioma are male, and patients commonly present with a pleural effusion associated with breathlessness and often accompanied by chest-wall pain (more than 60 percent of patients).[7] The combination of an unexplained pleural effusion and pleural pain should raise the suspicion of malignant mesothelioma, even if the initial cytologic findings are negative. Weight loss and fatigue are common later in the progression of pleural mesothelioma but are less so at presentation (occurring in less than 30 percent of patients).[7] Although a cytologic diagnosis can be made quickly,[10] malignant mesothelioma is usually not diagnosed until two or three months after the onset of symptoms; delays of this length are especially frequent in centers in which the disease is uncommon. Mesothelioma is occasionally discovered incidentally on routine chest radiography.

The most common presenting features in patients with peritoneal malignant mesothelioma are distention due to ascites, abdominal pain, and occasionally organ impairment, such as bowel obstruction.[11] In addition to the pleura and the peritoneum, mesotheliomas can occur on other serosal surfaces, such as the pericardium and the tunica vaginalis.[1,7] Because malignant mesothelioma develops covertly within the body cavities, patients usually have fairly extensive tumor involvement by the time they seek care. However, metastases are rarely the cause of death.[12] Local invasion, which is common, causes enlargement of the lymph nodes and may result in obstruction of the superior vena cava, cardiac tamponade, subcutaneous extensions (Fig. 1A), and spinal cord compression.[7] Miliary spread of malignant mesothelioma can also occur.[13] The contralateral lung or the peritoneal cavity is invaded by pleural mesothelioma in 10 to 20 percent of cases.[14]

The most common physical signs of malignant mesothelioma in the chest are related

Table 1. Worldwide Trends in the Epidemiologic Features of Malignant Mesothelioma.*

Country or Region	Incidence	Predicted Peak Year	Predicted No. of Deaths in Next 40 Yr†	Predicted Cost‡
	cases/million population			*billions of U.S. dollars*
United States	15	2004	72,000	200
Europe	18§	2015–2020	250,000	80
Japan	7	2025	103,000	—
Australia	40	2015	30,000	5–10

* The sources of the data on the incidence (most recent figures), predicted peak year, and predicted number of deaths in the next 40 years are as follows: United States, Roushdy-Hammady et al.[2]; Europe, Pelin et al.[3]; Japan, Sebastien et al.[4]; and Australia, Wagner et al.[5] The sources of the data on predicted cost are as follows: United States, Shah and Williams[6]; Europe, Lee et al.[7]; and Australia, Wagner et al.[5] Costs for Japan are unknown.
† The predicted number of deaths is estimated from data on annual incidence and predicted peak year.
‡ The costs shown are for compensation only; health care costs are excluded.
§ The incidence, in number of cases per million population, is 33 in Great Britain, 30 in the Netherlands, 15 in Germany, 16 in France, and 19 in Italy (range in Europe, 15 to 33).

to the underlying effusion (pleural effusion or ascites). Clubbing occurs in less than 1 percent of cases. When pleural mesothelioma progresses, the affected site becomes fixed and cannot expand. Such chest-wall fixation can lead to pneumonia. The physical signs in patients with peritoneal mesothelioma are typically distention and ascites. Subcutaneous masses are almost always associated with prior medical intervention and occur in thoracotomy wounds and previous drainage sites.

What is loosely known as a "cancer syndrome," consisting of weight loss, fatigue, cachexia, fevers and night sweats, thrombocytosis, hypoalbuminemia, an elevated erythrocyte sedimentation rate, and anemia,[7] is uncommon at diagnosis but often develops in patients later in the course of malignant mesothelioma. There is evidence that this syndrome is due to circulating interleukin-6 and that it can be reversed, at least in animals, even when the growth of the tumor continues unchanged.[15]

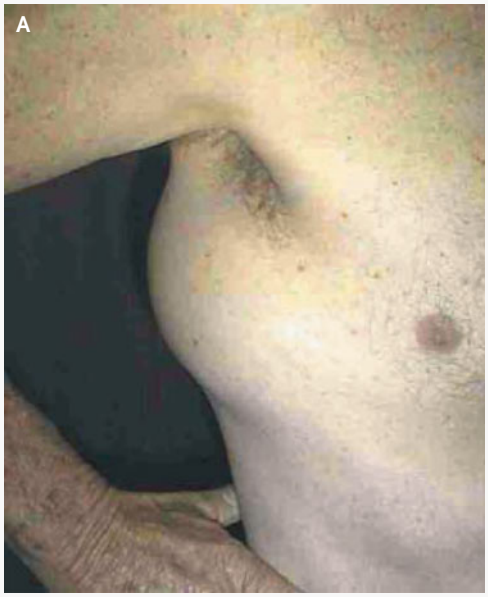
CAUSES

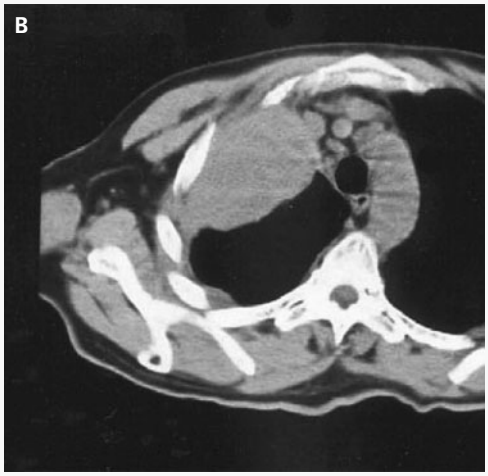
Asbestos is the principal carcinogen associated with malignant mesothelioma. Indeed, malignant mesothelioma was rare before the widespread use of asbestos. In 1960 the first convincing evidence of a link between malignant mesothelioma and both occupational and incidental asbestos exposure was reported, on the basis of data from South Africa.[5]

There are two principal forms of asbestos: long, thin fibers known as amphiboles, one type of which is called blue asbestos, and feathery fibers known as chrysotile or white asbestos. Whether only amphibole fibers cause malignant mesothelioma or whether chrysotile fibers can also cause mesothelioma is still debated.[16,17] The association of chrysotile with malignant mesothelioma was once thought to be due to contamination of chrysotile with the amphibole tremolite; however, current evidence, particularly from electron microscopical studies, supports the view that chrysotile itself can cause malignant mesothelioma, although at rates lower than those of mesothelioma caused by amphiboles.[18]

Malignant mesotheliomas occur initially on the parietal surface of the pleural mesothelium, rather than on the visceral surface.[19] Several mechanisms might account for this finding; one possibility is that the asbestos fibers stick out from the lung surface and cause repeated cycles of scratching, damage, inflammation, and repair in the adjacent parietal mesothelial-cell layer.

Simian virus 40 (SV40), a DNA virus, has been implicated as a cofactor in the causation of malignant mesothelioma.[20] This virus, which blocks tumor-suppressor genes, is a potent oncogenic virus in human and rodent cells; SV40 DNA sequences have been found in brain and bone tumors, lymphomas, and malignant mesotheliomas, as well as in atypical mesothelial proliferations and superficial noninvasive lesions of the mesothelium.[21] There is some evidence that SV40 may have been inadvertently transmitted to humans in injectable poliomyelitis vaccines 35 to 50 years ago. The putative involvement of SV40 in the pathogenesis of malignant mesothelioma has become a controversial issue,





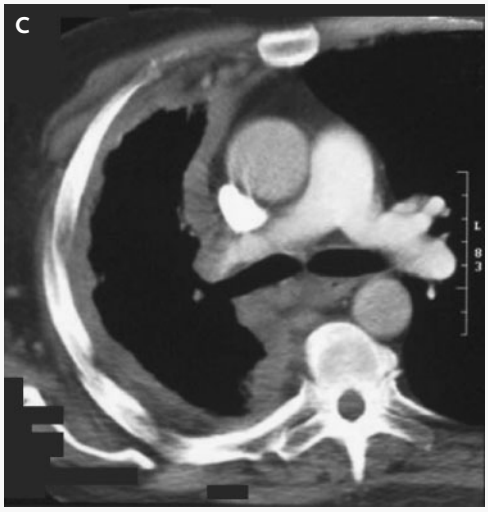


Figure 1. Clinical and Computed Tomographic (CT) Features of Malignant Mesothelioma.

Panel A shows a subcutaneous extension of malignant mesothelioma. Panel B shows the CT appearance of pleural mesothelioma consisting predominantly of a pleural mass, and Panel C shows its CT appearance as a diffuse, encircling rind of tumor.

and its role remains unclear and unproved.[22] In rare cases, malignant mesothelioma is caused by radiation or one of a small number of other factors.[23]

EPIDEMIOLOGIC FEATURES

The rising worldwide incidence of malignant mesothelioma is not expected to peak for another 10 to 20 years. It is possible that the disease has already reached its peak incidence in the United States,[24] whereas the anticipated peaks in Europe[25] and Australia[17] are not predicted to occur for another 10 to 15 years. Furthermore, in Japan and other non-Western countries, in which heavy use of asbestos occurred later than in the Western world, there is a corresponding delay in the anticipated peak incidence of mesothelioma (Table 1).[26] There is substantial concern that the increased use of asbestos in developing countries may result in an increase in the number of cases of malignant mesothelioma for many decades to come unless strong occupational health controls are put in place.[27]

Malignant mesothelioma has occurred in three principal cohorts of asbestos-exposed persons.[17] The initial cases occurred in people who were directly exposed to asbestos in their work, especially those exposed to blue asbestos during its mining or milling. The clearest and best-studied example of such exposure occurred at the blue-asbestos mine in Wittenoom, Australia, the site of one the worst industrial disasters in history. Not only were the miners heavily exposed to asbestos, but the soft asbestos tailings were used instead of grass to cover the schoolyards and playgrounds of the town, resulting in a huge outbreak of mesotheliomas, many in young adults who had played in the asbestos dust as children.[17] Subsequently, asbestos-related diseases were noted in other workers who were exposed later in the chain of manufacture and use of asbestos products, such as plumbers, carpenters, defense personnel, and installers of asbestos insulation. A third group of affected people, accounting

for 20 to 30 percent of current cases of malignant mesothelioma, consists of those who were exposed to asbestos unknowingly and incidentally in the myriad situations in which asbestos fibers are released into the atmosphere in industrialized countries.[8] There have been several reports of familial clustering of malignant mesothelioma, including one cluster showing a possible autosomal dominant pattern in subjects studied in Cappadocia, Turkey.[2]

PATHOGENESIS

Mesothelial cells normally facilitate the free movement of the pleural surfaces during respiration by enmeshing lubricating glycoproteins. These cells readily proliferate in response to injury and growth factors.[3] Asbestos presumably induces mutations in many of the estimated 2 billion mesothelial cells in adult humans.

There are four principal processes by which asbestos affects the pleura. First, asbestos fibers may irritate the pleura. The shape of asbestos fibers, particularly the ratio of their length to their width, determines how deeply into the lung they penetrate and their likelihood of inducing cancer. Fibers penetrating the lung may enter or irritate the pleura and induce disease[4] manifested by scarring (plaques) or a frank malignant process (malignant mesothelioma). Second, asbestos fibers may sever or pierce the mitotic spindle of cells and thereby disrupt mitosis, resulting in aneuploidy and other forms of chromosomal damage.[28]

Third, asbestos induces the generation of iron-related reactive oxygen species that cause DNA damage.[29] Fourth, asbestos induces phosphorylation of the mitogen-activated protein (MAP) kinases and of extracellular signal–regulated kinases (ERK) 1 and 2. Phosphorylation of these kinases increases the expression of early-response proto-oncogenes that encode members of the Fos–Jun and activator protein 1 families.[30]

BIOLOGY

Although the results are crude, conventional cytogenetic analysis has been used to investigate the pathogenesis of malignant mesothelioma. Abnormal karyotypes, often with extensive aneuploidy and structural rearrangements, have been described for a number of genetic loci. Loss of chromosome 22 is the most common gross change, but structural rearrangements of 1p, 3p, 9p, and 6q are often noted.[31,32]

Various animal models of malignant mesothelioma, mostly in rats and mice, have been described.[33] Murine models are particularly useful, because murine mesothelial cells respond to asbestos exposure in a fashion similar to that of human mesothelial cells.[33] Intriguingly, malignant mesothelioma reliably develops in hamsters in the absence of asbestos when they are injected with SV40 virus.[34] Animal models have also proved useful for preclinical testing of new therapies for malignant mesothelioma. Six features are common to most cancer cells, and there is evidence that all six are also found in malignant mesothelioma (Fig. 2).[35]

Growth Advantage

Mesothelioma cells exhibit increased or dysregulated growth. The cells produce and respond to many growth factors, including platelet-derived growth factors A and B,[36,37] epidermal growth factor,[38] and transforming growth factor β.[39,40] Recent studies using mesothelioma cell lines have suggested a role for the Wnt/frizzled-related protein pathway.[41] Mesothelioma growth can be stimulated by autocrine mechanisms and also by "private" pathways, whereby mesothelioma cells stimulate themselves internally by growth factors that they themselves produce.[37]

Immortalization by the Action of Telomerase

Telomere shortening has been called a "counting device for cell generations."[35] Ninety percent of malignant mesotheliomas express telomerase, which enables cells to avoid telomere shortening and thus to continue cell division (i.e., to become immortalized).[42]

Absence of Tumor-Suppressor Genes

Tumor-suppressor genes operate in various ways to block tumor growth. Although the two principal tumor-suppressor genes, *Rb* and *p53*, are not commonly absent in malignant mesothelioma, other molecules that are important in the *Rb* and *p53* pathways are involved, particularly *p16* and *p14*.[43,44] Another gene product in the tumor-suppressor gene pathway, NF2-merlin, is also important.[45]

Induction of Antiapoptotic Processes

Cells can die from activation of their death receptors by ligands such as tumor necrosis factor (TNF), TNF-related apoptosis-inducing ligand (TRAIL), and Fas ligand or as a result of blockade of growth factors, which leads to activation of the caspase

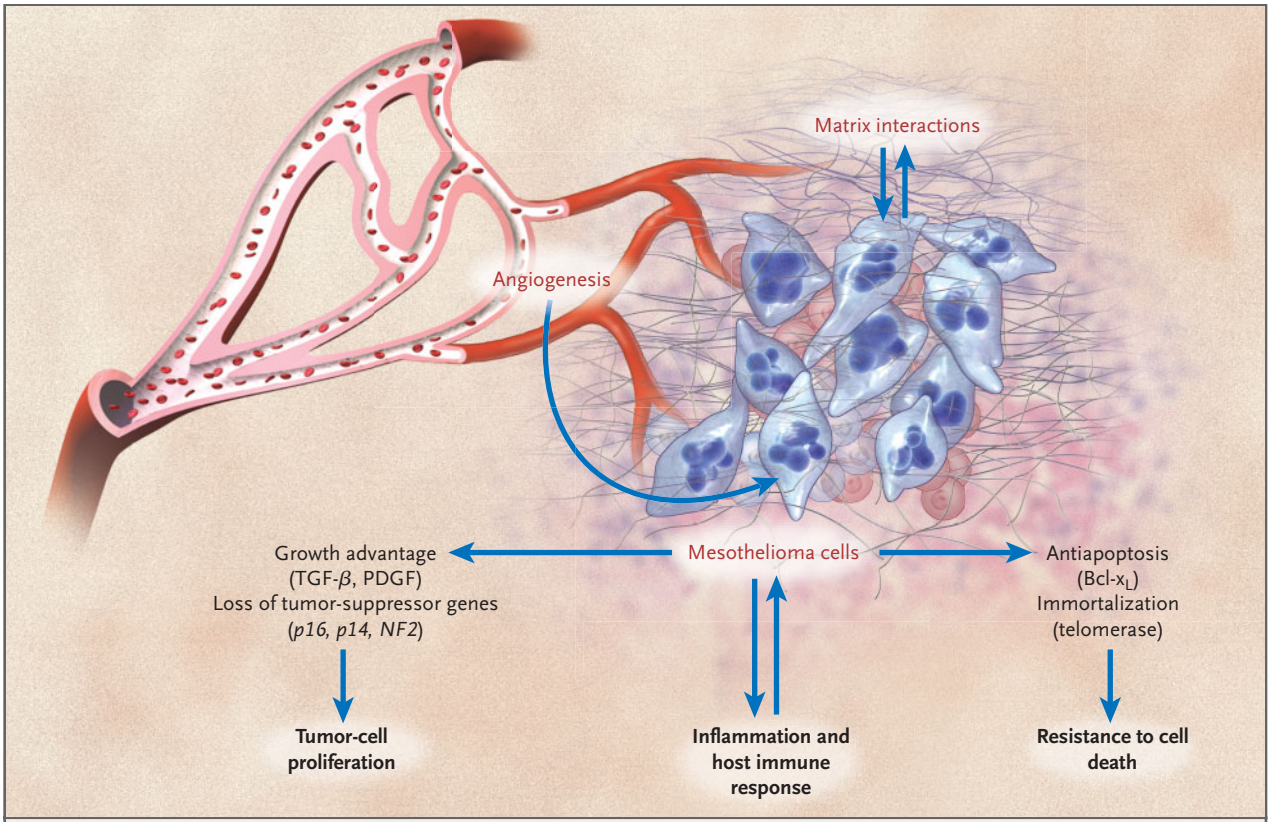


Figure 2. Key Biologic Features of Malignant Mesothelioma.
Mesothelioma-cell growth requires angiogenesis to provide nutrients and matrix interactions to provide a supportive environment. Growth signals and loss of tumor-suppressor genes provide the growth advantage that leads to tumor-cell proliferation. The host responds to mesothelioma with inflammation and immunity. Antiapoptosis and immortalization render such cells resistant to cell death. Although the overall events are likely to be similar, the particular molecular lesions that are acquired probably vary from patient to patient. Each patient probably has many mesothelial cells that carry different patterns of mutations. Only one of these cells may undergo the final crucial molecular changes that produce malignant mesothelioma, and this cell may then seed the rest of the pleural cavity. TGF-β denotes transforming growth factor β, PDGF platelet-derived growth factor, and *NF2* the gene encoding neurofibromatosis type 2.

death cascade.[46] The activity of the antiapoptosis molecule Bcl-x_L is elevated in malignant mesothelioma cells, and synergism between death-receptor ligation and chemotherapy has been described in cells from patients with malignant mesothelioma.[47]

Increased Angiogenesis

Because their cells are avid for nutrients, tumors require the continuous formation of new blood vessels in order to grow.[35] Malignant mesothelioma cells produce angiogenic factors, such as vascular endothelial growth factor (VEGF).[48] Moreover, VEGF blockade reduces mesothelioma growth in animal models.[49] Increased vascularity in mesothelioma-biopsy specimens is associated with a worse prognosis, as compared with those in which vascularity is not increased.[50]

Matrix Interactions

Malignant mesothelioma exists in a collagenous environment, and it is likely that its growth is related to its interactions with and regulation of this environment. Malignant mesothelioma cells make collagen, and the prognosis of mesothelioma appears to be related to the expression of matrix metalloproteinases.[51,52]

Malignant mesothelioma tumors induce responses from their hosts. Chronic inflammation occurs, manifested by the presence of inflammatory cells and cytokines. The inflammation is due

both to the asbestos and to the malignant process itself.[53] The host also commonly mounts a weak antitumor immune response to undefined mesothelioma proteins[54] as well as to overexpressed common proteins, such as p53.[55]

ADVANCES IN DIAGNOSIS

Accurate and rapid diagnosis of malignant mesothelioma is important for therapeutic and medicolegal reasons. The most frequent diagnostic problem is the differentiation of malignant mesothelioma from adenocarcinoma — a distinction that is particularly difficult to make when the tumor has invaded the pleura.[56]

CYTOLOGIC ANALYSIS

Cytologic evidence of malignant mesothelioma in the pleural or ascitic fluid is found in 33 to 84 percent of cases.[57] In some patients, sampling by fine-needle aspiration of the tumor is required to make a diagnosis of malignant mesothelioma, particularly when there is no effusion. A group of immunohistochemical markers is important in the differential diagnosis of malignant mesothelioma. As the first step, a marker such as calretinin or the Wilms' tumor 1 antigen (WT1) is used to determine whether the tissue is mesothelial (Fig. 3A and 3B). The second step is to use a marker such as epithelial membrane antigen (EMA; also known as CA15-3 and mucin-1) to determine whether the tissue is malignant. Staining for EMA in a thick peripheral distribution is highly suggestive of malignant mesothelioma (Fig. 3C).[58,59] Of the two anti-EMA antibodies, E29 has significantly greater specificity than MC-5.[59] In experienced hands, cytologic analysis is sufficient to make a diagnosis with a high level of confidence in approximately 80 percent of cases of malignant mesothelioma.[60]

HISTOPATHOLOGICAL ANALYSIS

Because cytologic findings may be inconclusive or pleural or ascitic fluid may be absent altogether, tumor biopsy is often needed. Closed biopsy (e.g., with the use of an Abrams' needle) is less likely than direct thoracoscopic biopsy to yield positive results. Immunohistochemical staining to show, for example, expression of epithelial membrane antigen on the luminal aspects of the tumor is essential in the diagnostic process.[56] Cytokeratin staining helps to confirm invasion and to distinguish malignant mesothelioma from sarcoma and melanoma. Malignant mesothelioma is distinguished from adenocarcinoma by the use of specific antibodies. Malignant mesothelioma is characterized by the presence of staining for EMA, calretinin, WT1, cytokeratin 5/6, HBME-1 (an anti–mesothelial cell antibody), or mesothelin (more than 85 percent of epithelioid

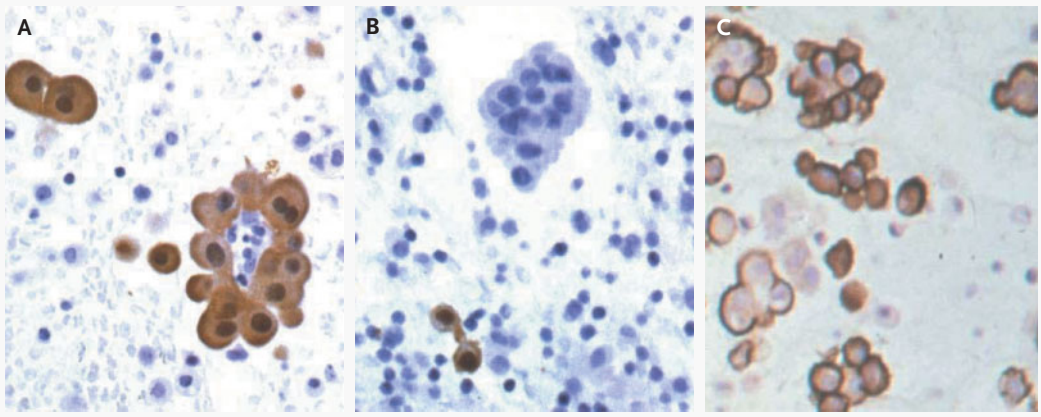


Figure 3. Cytopathological Features of Malignant Mesothelioma.

Cytologic cell-block samples of pleural fluid show positive staining for calretinin in a mesothelioma sample (Panel A) and negative staining in an adenocarcinoma sample (Panel B), except for a few benign mesothelial cells, which stain positive. In experienced hands, staining for epithelial membrane antigen in a peripheral distribution (Panel C) can establish the diagnosis of malignant mesothelioma. Images courtesy of Drs. A. Segal and D. Whitaker.

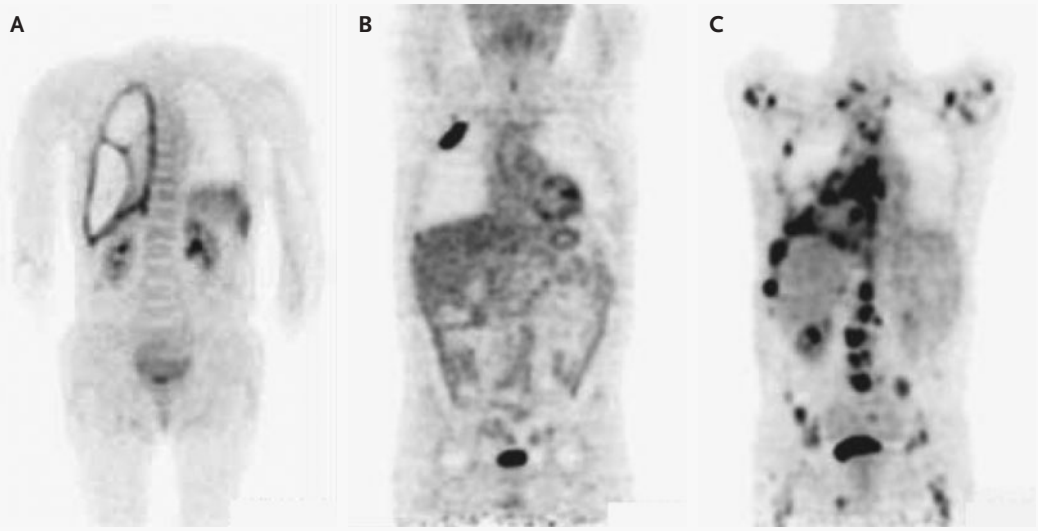


Figure 4. Features of Malignant Mesothelioma on Positron-Emission Tomography (PET).
Shown are several patterns seen in malignant mesothelioma. PET images can demonstrate diffuse uptake of ^{18}F-fluorodeoxyglucose in an encircling pattern (Panel A) or in a localized nodular pattern (Panel B), with both patterns resembling those seen on CT, or it can demonstrate extensive uptake in addition to metastases that extend beyond the tumor limits defined by CT (Panel C). Images courtesy of Dr. A. van der Schaff.

malignant mesotheliomas are positive for mesothelin) and the absence of staining for antigens such as carcinoembryonic antigen; thyroid transcription factor-1; the tumor glycoproteins B72.3, MOC-31, and Ber-EP4; and the epithelial glycoprotein BG8. Furthermore, other tumors can stain positive with these antibodies (e.g., ovarian carcinoma stains for mesothelin and WT1). Electron microscopy is a useful additional method by which to distinguish malignant mesothelioma from adenocarcinoma or to distinguish desmoplastic or sarcomatoid mesothelioma from fibrous pleuritis.[56] Mesothelioma in situ (atypical mesothelial proliferation) is hypothesized to be the earliest lesion, akin to cervical dysplastic lesions.[60]

IMAGING

Conventional chest radiography at presentation typically shows pleural effusion and occasionally shows a pleural-based mass. Patients who initially present with an advanced tumor have an encircling rind of tumor; extensive, lobulated, pleural-based tumor masses; or both.[61] Plaques (benign pleural fibrotic sheets) are a sign of asbestos exposure but are not a precursor to malignant mesothelioma.

Computed tomographic (CT) scanning at presentation often shows pleural effusion alone (74 percent of cases) or pleural-based masses (92 percent of cases) (Fig. 1B), with or without thickening of the interlobular septa (86 percent of cases).[61] Invasion of the chest wall is seen in only 18 percent of patients, usually after intervention. CT scanning also is used to identify signs of asbestos exposure, such as plaques (present in 20 percent of cases). It is not known why some forms of malignant mesothelioma produce mainly localized masses (Fig. 1B), whereas others grow as a uniform rind of tumor encasing the lung[62] (Fig. 1C).

Magnetic resonance imaging (MRI) is useful in determining the extent of malignant mesothelioma, particularly when the tumor invades local structures such as the ribs and the diaphragm.[62] It may also be helpful in planning radiotherapy for localized disease, such as spinal cord mesothelioma.

Positron-emission tomography (PET) is used to distinguish benign from malignant pleural masses. It also appears to be useful for detecting extrathoracic disease, particularly lymph-node involvement, and hence has a role in the staging of tumors.[63] Different patterns of marker uptake are seen, some of

Table 2. Frequency of Elevated Levels of Serum Mesothelin-Related Protein (SMRP) in Patients with Malignant Mesothelioma and Other Pulmonary and Pleural Diseases.*

Disease	Total No. of Patients	No. of Patients with Elevated SMRP
		%
Mesothelioma		
At diagnosis	20	75
At any stage	44	84
Pleural disease		
Plaques or thickening	18	0
Inflammation	12	0
Other cancer	6	0
Nonpleural lung cancer	30	3
Nonpleural lung inflammation		
Asbestosis	22	5
Other inflammation	61	2

* SMRP in serum was assayed by a double-determinant enzyme-linked immunosorbent assay. Elevated levels are defined as those more than 2 SD above the mean for healthy persons. Data are from Robinson et al.,[65] where definitions of patient subgroups can also be found.

which provide additional information about the extent of the disease that is not obvious on CT scans (Fig. 4). Hypermetabolic lymph-node involvement is often seen in lymph nodes that appear normal on CT scans.[63] High standardized uptake values correlate with a worse prognosis and also help to differentiate tumor from fibrosis and necrosis in some patients.[64] It has been suggested that the results of PET combined with CT scanning more accurately reflect the likely response to chemotherapy than do the results of either PET or CT scanning alone; however, this suggestion requires further evaluation in randomized trials.[64]

SERUM MARKERS

Serum mesothelin–related protein (SMRP) is a soluble form of mesothelin. The SMRP level is elevated in 84 percent of patients with malignant mesothelioma and in less than 2 percent of patients with other pulmonary or pleural diseases[65] (Table 2). More than 60 percent of patients with malignant mesothelioma have elevated SMRP levels at the time of diagnosis. Measurement of SMRP levels is probably best used as an adjunct to cytopathological and histopathological examination in the diagnosis of malignant mesothelioma; early thoracoscopic sampling is important. Since SMRP levels increase with the progression of mesothelioma and decrease with its regression or with resection of the tumor, they may be useful in monitoring therapy. SMRP levels may prove useful in screening for malignant mesothelioma; several previously healthy persons who had been exposed to asbestos and who had elevated SMRP levels subsequently presented with malignant mesothelioma one to six years after their blood tests.[65]

Other potentially useful serum markers currently being analyzed include CA 125, CA 15-3, and hyaluronic acid. Osteopontin has also recently been shown to be a marker of malignant mesothelioma.[66] These markers may have a role in paired analyses to improve the specificity or sensitivity of SMRP measurements.

Mass spectrometric analysis of serum proteins, serologic analysis to identify antigenic malignant mesothelioma proteins, and serial analysis of gene expression are some of the techniques currently being used to identify other potentially useful markers.[67]

OTHER BLOOD TESTS

Patients with malignant mesothelioma, especially those with progressive disease, often have the nonspecific features of anemia of malignant disease: thrombocytosis, an increased erythrocyte sedimentation rate, and elevated gamma globulin levels.[7] Abnormal results of liver-function tests are common, and hypoalbuminemia often occurs with advancing disease and contributes to marked peripheral edema.[68]

PULMONARY-FUNCTION TESTS

A restrictive pattern with increased maximal expiratory flow rates is typical in patients with malignant mesothelioma. A change in forced vital capacity is a surprisingly accurate and simple indication of disease progression or regression, provided there are no changes in the amount of pleural fluid.[69]

DNA MICROARRAY STUDIES

Microarray techniques make it possible to measure simultaneously the expression of thousands of genes in one tumor sample. Such studies have revealed expression patterns associated with the genesis and progression of some cancers.[70] A preliminary study comparing 16 mesothelioma tumors with 4 normal pleural samples showed a coordinated up-regulation of the expression of genes associat-

ed with energy, protein translation, and cytoskeletal remodeling pathways.[71] In a separate microarray study designed to address the difficult pathological distinction between adenocarcinoma of the lung and pleural malignant mesothelioma, Gordon et al. reported that this distinction could be made with 99 percent accuracy by measuring the expression levels of three pairs of genes; the measurements were extensively verified by quantitative polymerase-chain-reaction analysis and immunohistochemical analysis.[72] The genes involved included those encoding for calretinin and TTF-1, which are already widely used in immunohistochemical analysis for the differentiation of malignant mesothelioma from lung cancer.

PROGNOSTIC FACTORS AND STAGING

The median survival of patients with malignant mesothelioma from the time of diagnosis is 12 months.[1] The prognosis is worse in male patients and in patients with extensive disease, poor performance status (e.g., according to Eastern Cooperative Oncology Group or Karnovsky scores), elevated white-cell counts, anemia, thrombocytosis, sarcomatoid histologic findings, or high standardized uptake value ratios on PET.[66,73,74] Expression of certain biochemical markers (cyclooxygenase-2 and VEGF), as well as hypermethylation of the *P16^{INK4a}* gene, increased vascularity, and evidence of SV40 virus in the tumor, also indicate a worse prognosis.[66,73,74]

The International Mesothelioma Interest Group has published a modified tumor–node–metastasis system that is used to predict prognosis.[75] CT, MRI, PET, and often thoracoscopy and mediastinoscopy are all useful in preoperative assessment; which techniques are used often differs among centers. Final staging requires surgery.[76]

ADVANCES IN TREATMENT

SURGERY

Surgery has proved most useful for palliation — for example, for local control of recurrent effusions. Debulking surgery is used in some centers. Recent experience has shown that video-assisted thoracoscopic pleurectomy is possible.[77] The consensus among centers is that surgery, whether debulking surgery or radical resection (extrapleural pneumonectomy), is best performed in combination with adjuvant chemotherapy, radiotherapy, immunotherapy, or other treatment.[77-80]

CHEMOTHERAPY

Until recently, all reviews of chemotherapy for malignant mesothelioma reported poor response rates (typically less than 15 to 20 percent) and, because of these low rates, did not recommend a standard of care.[81] However, a number of multicenter studies are now under way, and several new therapeutic regimens appear to be useful.

Pemetrexed is a potent inhibitor of a number of proteins, including thymidylate synthase and dihydrofolate reductase, both of which are required for DNA synthesis. In a multicenter phase 3 study involving 448 patients, those treated with pemetrexed plus cisplatin had a longer overall median survival (12.1 months) than those treated with cisplatin alone (9.3 months) and had an objective response rate (shrinkage of the tumor by at least 50 percent) of 41 percent.[82]

Treatment with gemcitabine, a "false nucleotide" that is incorporated into DNA, plus cisplatin resulted in objective response rates of 48 percent and 33 percent in two studies, as well as symptomatic improvement and quality-of-life benefits.[83] Imatinib (Gleevec) and gefitinib (Iressa) block the platelet-derived growth factor and epidermal growth factor signaling pathways, respectively. Both of these pathways are active in malignant mesothelioma. Early studies of the treatment of mesothelioma with these compounds, however, have yielded no convincing evidence of a response.[84]

RADIOTHERAPY

Malignant mesothelioma is resistant to traditional radiotherapy.[85] Local radiotherapy directed to surgical sites prevents seeding of tumor, and radiotherapy can provide palliative relief of somatic chest-wall pain.[85] The diffuse nature of the tumor, which often covers most of the lung and the interlobular fissures, is the principal limitation to radiotherapy. However, even when the affected lung is removed, radiotherapy is of limited effectiveness.[86]

The most successful fractionation method is intensity-modulated radiotherapy,[86] a technique generally used after radical surgical resection of malignant mesothelioma. This approach controls local recurrence, but many patients die of metastatic disease.[86] The use of radioactive colloids and other

forms of brachytherapy in the pleural or peritoneal cavity is logical, but the results have been disappointing.[87]

IMMUNOTHERAPY

Both studies in animals and clinical trials of immunotherapy suggest that malignant mesothelioma is sensitive to immunotherapy. Trials of interferon alfa, intrapleural interleukin-2, and intratumoral granulocyte–macrophage colony-stimulating factor have shown some tumor response, but nothing that warrants widespread use of these agents.[88-92]

GENE THERAPY

Gene therapy for cancer generally involves the administration of engineered viruses to patients. In a small study, six patients with treatment-resistant malignant mesothelioma received intratumoral injections of a vaccinia vector containing the interleukin-2 transgene in an attempt to modulate the immune response. This treatment induced a lymphocytic infiltrate and a surprisingly persistent, though low-level, expression of the transgene, with no major tumor regressions.[93] "Suicide gene" therapy — that is, delivery of a viral vector encoding a viral thymidine kinase, which renders the cell sensitive to the drug ganciclovir by converting the drug to a toxic metabolite — has also induced some responses in patients with malignant mesothelioma.[94]

OTHER THERAPIES

In photodynamic therapy, light acts on a sensitizing drug to generate reactive oxygen species that induce cellular necrosis. This treatment is labor intensive. It induces cytoreduction in malignant mesothelioma, although it has not been associated with impressive long-term responses.[95]

Studies are being conducted on several antiangiogenic agents that target the vascular VEGF pathway, such as bevacizumab, thalidomide, BAY43-9006, and PTK787, as well as other agents that block specific mesothelioma pathways, including the histone deacetylase inhibitor superoylanilide hydroxamic acid.[96] Proteosome inhibitors, other histone deacetylases, and other VEGF antagonists,[96] as well as antimesothelin monoclonal antibodies labeled with toxins, are also being investigated for the treatment of malignant mesothelioma.[97]

Recent studies in animal models indicate that advanced malignant mesothelioma can be cured in the majority of cases in which an apoptosis-inducing agent (e.g., gemcitabine) is combined with an immunotherapeutic approach that targets the antigen-presenting cell (e.g., the use of antibodies directed at the CD40 molecule).[98] Chemotherapeutic agents are also synergistic with TRAIL agonists in mesothelioma cells.[47]

PALLIATION

Recurrent pleural effusions are best controlled by the removal of all fluid, with the use of suction when required, followed by talc application or surgical pleurodesis.[68]

There are several types of pain in patients with malignant mesothelioma.[68] Local involvement of the chest wall causes somatic pain. Intercostal nerve or vertebral invasion causes neuropathic pain. Organ invasion causes more diffuse visceral pain. Pain control can be difficult. Opiates should provide adequate pain relief for the duration of action of the drug (4 hours for liquid morphine and 12 hours for sustained-release morphine), without unnecessary side effects. Somatic pain often responds to a nonsteroidal antiinflammatory drug given in addition to an opiate. Neuropathic pain requires the addition of an anticonvulsant, such as carbamazepine or sodium valproate. Some patients require procedural pain relief, such as intrathecal analgesia or nerve block.

Dyspnea due to fluid accumulation or encasement of the lung by tumor is common.[68] Opiates are useful after any reversible causes of dyspnea, such as accumulation of fluid and anemia, have been dealt with.

Psychosocial factors are important in the palliation of malignant mesothelioma. Patients often express anger and fear, which are compounded by the medicolegal process. Involvement of a team of professional and community caregivers is very effective.[68]

CONCLUSIONS

The increasing worldwide incidence of malignant mesothelioma will result in the death of hundreds of thousands of people and should provide a strong moral imperative for urgent, focused research. In addition, the enormous compensation costs of mesothelioma provide an economic incentive.

Advances in the treatment of this difficult dis-

ease will occur only when science can push beyond the skepticism and pessimism that have been associated with malignant mesothelioma. The past 10 to 15 years have seen important advances in the diagnosis and management of this disease. The highly interactive and cooperative international mesothelioma research network is well placed to make further advances.

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