

Mesothelioma and Asbestos-Related Pleural Diseases

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Key Words

Asbestos · Mesothelioma · Plaque · Pleural effusion · Pleural cancer · Rounded atelectasis · Pleural fibrosis

Abstract

At present, the use of asbestos is not regulated at a world-wide scale. Moreover, there is a latency period between asbestos exposure and the manifestations of asbestos-related diseases. Consequently, pulmonologists are still dealing with consequences of asbestos exposure, which mainly occur at the pleural surface. The aim of this review is to provide an overview of asbestos-related pleural diseases. We summarized the most relevant data for the diagnosis and the management of benign asbestos pleural effusions, pleural plaques, diffuse pleural thickening and rounded atelectasis. Special attention is dedicated to malignant pleural mesothelioma, given the challenging issues of this disease, the recent advances in its management and the dynamism of research in this area.

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Introduction

Asbestos is the name given to a group of naturally occurring silicate minerals, whose fire-resistant properties have been known for thousands of years. Asbestos deposits are widely distributed throughout the world, most of them in mountain-forming regions. Techniques for spinning and weaving the fibers were developed in the 19th century and led to a rapid increase in their use. Asbestos is a good thermal and electrical isolator and is durable, strong and flexible. That is the reason why asbestos was extensively used in different commercial settings, such as insulation materials, brake pads and linings, household products, floor tiles, electric wiring, paints and cements.

Asbestos fibers can be categorized into 2 main groups, the serpentines and the amphiboles [1]. Serpentine fibers are curly, pliable, easily shred into finer particles and subject to dissolution in tissues. The most important serpentine fiber is chrysotile (white asbestos). Amphiboles are rigid fibers, sharp and highly resistant to chemical and biological dissolution. There are 5 members: 2 which can be used commercially, i.e. crocidolite (blue asbestos) and amosite (brown asbestos), and 3 non-commercial fibers that can be found as contaminants in other mining operations, i.e. tremolite (a common contaminant of chrysotile), anthophyllite (a common contaminant of industrial talc) and actinolite.

It is at the pleural surface where the effect of past asbestos exposure is most often found. There are 4 types of benign pleural reactions: (1) benign asbestos pleural effusions (BAPEs); (2) pleural plaques, local areas of fibrosis of the parietal pleura; (3) diffuse pleural thickening (DPT), and (4) rounded atelectasis, which occurs when an area of visceral pleural fibrosis extends into the lung parenchyma and renders a portion of the lung airless. There is also mesothelioma, a primary malignancy of the pleura (and occasionally the peritoneum). These 5 asbestos-related pleural diseases will be detailed in this review, while other consequences of asbestos exposure, such as asbestosis, which is fibrosis of the lung parenchyma, and lung cancer, will not be included.

Benign Asbestos Pleural Effusion

Benign pleural effusion related to previous asbestos exposure was first described in 1964 [2]. It is a common asbestos-related pleuropulmonary abnormality during the first 20 years following exposure; however, it may occur from 1 to 60 years from initial exposure [3–5]. BAPE is defined as an effusion that occurs in the setting of asbestos exposure, in the absence of other conditions, and is not followed by the development of malignancy within 3 years [6]. Using this definition, Epler et al. [3] reported an incidence of 9.2, 3.9 and 0.7 effusions per 1,000 person-years after heavy, moderate and mild asbestos exposure, respectively. However, the incidence of BAPE is probably underestimated, because most of the cases are asymptomatic [3, 5]. When symptomatic, pleural effusion may manifest with fever, cough, pleuritic-type pain and dyspnea [5]. The effusions are usually small to moderate in size and unilateral, but may be massive or bilateral (in approximately 10% of cases) and occasionally subside on one side only to recur on the other [3, 5].

The most sensitive imaging modality for detecting pleural fluid is a chest CT scan, while the addition of MRI is not particularly useful in this context [7]. BAPEs generally conform to the criteria of Light for an exudate [5, 8, 9], but have a variable composition: the fluid is often macroscopically hemorrhagic, of mixed cellularity, or with an increased eosinophilic count [5]. Asbestos bodies (asbestos fibers enveloped by an iron-containing protein coat) are seldom [10] or never [11] found in pleural fluid, may be occasionally seen in pleural tissue, and are frequently present in underlying lung tissue [10].

An unexplained pleural effusion, especially in asbestos-exposed subjects, should be sampled for chemical,

bacteriological and cytological analyses. Unless the findings are diagnostic, thoracoscopy should be performed in order to do pleural biopsies under visual control for histological examination. Indeed, all other causes of pleural effusion, and in particular malignancies, must be excluded before concluding to a BAPE.

BAPE does not require specific treatment, except thoracentesis if the patient presents symptoms. The natural history of BAPE is one of chronicity with frequent recurrences. Usually, the effusions subside slowly and spontaneously over a prolonged period, ranging from 1 to 17 months [4, 5, 9, 12]. Resolution results typically in a blunted costophrenic angle (80–90%), with DPT in approximately 50% of patients [13]. Recurrences are frequent (30–40%) and usually occur within 3 years of the initial presentation [3, 9].

A prolonged follow-up is necessary for asbestos-exposed patients with pleural effusions, sometimes including redo thorascopies. BAPE does not have specific prognostic implications with respect to the subsequent development of malignant pleural mesothelioma (MPM) [9, 14], but is the witness of exposure to the main risk factor of this malignancy.

Pleural Plaques

Pleural plaques are common manifestations of asbestos exposure. They are discrete elevated areas of hyaline fibrosis arising from the parietal pleura. There is a latency of 20–30 years between asbestos exposure and the development of pleural plaques [15]. The prevalence of pleural plaques is very low in non-asbestos-exposed populations, while it ranges from 0.53 to 8% in environmentally exposed populations [16]. Studies of occupationally exposed subjects reported a prevalence of 3–14% in dockyard workers and up to 58% in insulation workers [3, 16]. However, prevalence data must be regarded with caution, because much depends on the method employed for pleural plaque detection. The pathogenesis of pleural plaques remains unclear; several theories have been suggested but not validated [17, 18].

Microscopically, pleural plaques consist of acellular bundles of collagen in a undulating ‘basket weave’ pattern and may contain abundant numbers of asbestos fibers, almost exclusively chrysotiles, whereas asbestos bodies are absent [15, 19]. Macroscopically, pleural plaques have a white and shaggy appearance. Anatomically, they tend to lie adjacent to relatively rigid structures such as the ribs, the vertebral column and the tendinous

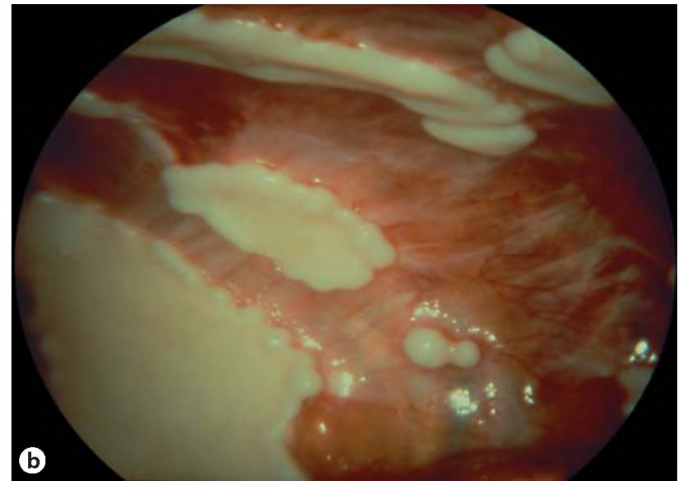
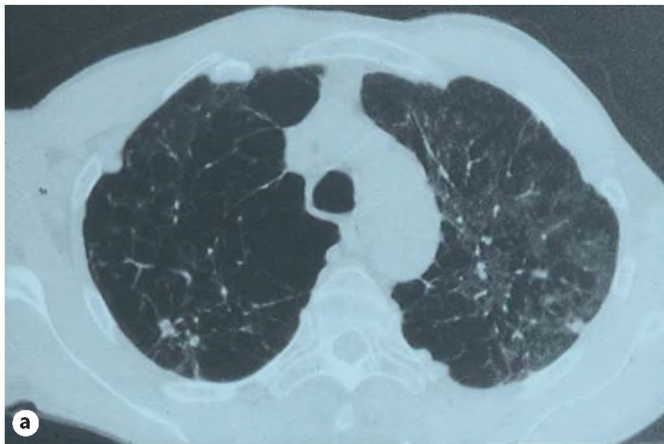


Fig. 1. Radiological (a) and thoracoscopic view (b) of benign asbestos pleural plaques on the parietal pleura. There is a non-specific lymphangitis between the plaques. Pleural biopsies have to be done at the level of non-specific inflammation to rule out an early-stage malignant mesothelioma.

part of the diaphragm. According to radiographic studies, the classic distribution of pleural plaques is the posterolateral chest wall between the seventh and the tenth ribs, the lateral chest wall between the sixth and the ninth ribs, the dome of the diaphragm and the mediastinal pleura (particularly above the pericardium) [20]. The apices and costophrenic angles are typically spared. CT findings support this distribution, but also show anterior and paravertebral plaques that are not well demonstrated at chest X-ray. The size and the number of pleural plaques vary: occasionally, plaques can be solitary but are most often multiple and bilateral. Some authors reported a left-sided predominance [21], whereas others found none [22]. Calcium deposition occurs in long-standing pleural plaques [3]. Fine, punctuate, irregular nodules are an early sign. The flecks of calcium gradually coalesce with the formation of dense streaks or plate-like deposits.

Pleural plaques are typically incidental imaging findings (fig. 1). The International Labour Office established a classification system for rating posteroanterior chest X-rays for pleural and parenchymal abnormalities of pneumoconioses [23]. The sensitivity for detecting pleural plaques on chest X-ray depends on their size, location, shape, degree of calcification and the technical quality of the radiograph [15]. Autopsy studies reported a high false-negative rate for the radiographic detection of pleural plaques [24–27]. Conversely, normal anatomic structures, such as extrapleural muscles and fat, may lead to false-positive diagnoses in up to 40% of cases [16, 25]. The

addition of bilateral oblique projections was reported to increase the detection of pleural diseases [28]. However, this technique is hardly used nowadays, since a CT scan was demonstrated to be more sensitive than a chest X-ray for the detection of pleural disease, especially for pleural plaques, which appear on CT as circumscribed areas of pleural thickening with well-demarcated edges [29–31]. Moreover, it was reported that high-resolution CT is more sensitive than conventional CT for detecting pleural abnormalities [32–34].

Pleural plaques are usually asymptomatic. Their impact on lung function has been the subject of several reports and conflicting results. Jones et al. [35] reviewed 36 studies conducted between 1965 and 1988 and concluded that limited or circumscribed pleural plaques are not associated with clinically significant reductions in pulmonary function. On the other hand, associations between pleural plaques and impairments in pulmonary function (vital capacity, diffusing capacity, exercise capacity) were reported [36, 37]. However, a recent study conducted in asbestos-cement factory workers did not find any correlation between the presence or the extent of pleural plaques and pulmonary functional parameters [38].

Pleural plaques do not undergo malignant degeneration into MPM, and their presence does not increase the risk of developing asbestos-related malignancy [39, 40]. However, they are the markers of asbestos exposure, which is a well-known risk factor of MPM and lung cancer.

Diffuse Pleural Thickening

DPT results from the fibrosis of the visceral pleura, with fusion to the parietal pleura [41]. Many studies showed that DPT is a consequence of BAPE [3, 42–44]. However, DPT is not a pathognomonic marker of asbestos exposure: many other causes of exudative pleural effusion can lead to DPT.

In asbestos-exposed subjects, DPT is markedly less frequent than pleural plaques. In a Finnish study among asbestos-exposed workers, the prevalence of pleural plaques was 27%, while the prevalence of DPT was 7% [45]. Histologically, there are similarities between DPT and pleural plaques, notably the 'basket weave' fibrous structure and the limited cellular fibroblastic activity. However, there is no fusion of the 2 pleural layers in pleural plaques. While pleural plaques are frequently bilateral and discrete localized lesions, DPT is rarely bilateral and often covers a wide area of the pleural surface [41]. DPT due to asbestos exposure rarely calcifies [20]. It can involve interlobar fissures, whereas pleural plaques normally show no involvement [20].

McLoud et al. [42] defined DPT on chest X-ray as a smooth non-interrupted pleural density that extends over at least one quarter of the chest wall, with or without obliteration of the costophrenic angle. On CT scan, DPT was defined as a continuous sheet of pleural thickening more than 5 cm wide, more than 8 cm in craniocaudal extent, and more than 3 mm thick [46]. As with pleural plaques, the CT scan is more sensitive and specific than chest X-ray in the detection of DPT [29, 31, 33].

Conversely to pleural plaques, DPT can lead to symptoms, notably to localized chest pain [47]. Moreover, DPT can cause significant restrictive ventilatory impairment [31, 35, 48–51]. Copley et al. [52] studied correlations between the extent of DPT (using different methods for measuring the area and thickness of abnormal pleura) and pulmonary functional parameters: they found a significant inverse relationship with the forced vital capacity and the total lung capacity.

Rounded Atelectasis

A unique form of pleural thickening is known as rounded atelectasis, folded lung, asbestos pseudotumor or Blesovsky syndrome [53]. This type of pleural involvement is less frequent than pleural plaques or DPT in asbestos-exposed subjects. There is a strong association between rounded atelectasis and asbestos exposure [54, 55],

but any cause of an organizing pleural exudate may be responsible for rounded atelectasis [55, 56]. The pathogenesis of rounded atelectasis is unclear, and several theories have been suggested. However, the most consensual one is an injury that leads to an inflammatory reaction and subsequent fibrosis in the most superficial layer of the visceral pleura [53, 57]. As the fibrous tissue matures, it contracts causing the pleura to buckle into the lung, resulting in atelectasis at this point.

On chest X-ray, rounded atelectasis appears as a peripheral mass-like opacity, which develops at one (and occasionally at several) location(s) [58]. A chest CT scan is more useful for diagnosis thanks to 3 major features [59]: (1) rounded or oval mass, 3.5–7 cm in diameter, abutting a peripheral pleural surface; (2) the curving 'comet tail' of bronchovascular structures passing into the mass, resulting in a blurred central margin, and (3) thickening of the adjacent pleura with or without calcification, which is usually thickest next to the mass. Volume loss in the adjacent lung is often, but not invariably, apparent [54]. The commonest sites for rounded atelectasis are the lingula, the middle lobe and the lower lobes [55], but any lobe can be involved, and bilateral involvement is not rare [59]. Radiologically, the distinction may sometimes be difficult between rounded atelectasis and primary lung cancer, which is the main differential diagnosis [1].

Patients with rounded atelectasis are asymptomatic in most cases, but can present with dyspnea if the atelectatic volume is large and lung function is compromised [60].

Malignant Pleural Mesothelioma

Epidemiology

MPM is an aggressive tumor, whose main etiology is the exposure to asbestos fibers. Exposure to amphibole fibers is much more likely to induce MPM than chrysotile fibers [61, 62]. If short exposures can lead to MPM, the tumor is mostly the consequence of long-time exposure [63, 64]. Although asbestos exposure can be environmental [65–67], most cases result from occupational exposures. That is the reason why the incidence of MPM shows marked differences between countries [68]. The highest incidence rates were reported in, or estimated for, Australia [69], Belgium [68] and Great Britain [70], with approximately 30 cases per million yearly. The occurrence of MPM parallels the exploitation and use of asbestos, with a mean latency period of 40 years or more [71–73].

Thus, the incidence of MPM is increasing throughout most developed countries and is expected to rise in the next 15 years in Europe [74] and to reach a peak in the United States in 2010 [75]. Although the incidence of MPM should then decrease in the developed countries, it will still increase in the developing countries, in which the use of asbestos is regulated poorly or not at all [76]. Consequently, MPM will remain a major health problem for many years on a worldwide scale.

Diagnosis

Clinical Presentation. Most patients with MPM are males and 50–70 years old [77]. Their initial clinical presentations are usually unilateral chest pain and dyspnea [78]. Constitutional symptoms such as fatigue and weight loss can occur [79], but generally, these appear later in the course of the disease. Occasionally, patients have no symptoms and their pleural disease is fortuitously found on a chest X-ray. Physical examination findings are most often consistent with a pleural effusion. A fixed hemithorax is suggestive of MPM, but is a relatively late sign. Signs of locoregional invasion, such as chest wall mass, pericardial effusion, superior vena cava obstruction, Horner's syndrome, spinal cord compression, phrenic nerve compression and esophageal compression are rare at presentation [80].

Imaging. The radiographic manifestation of MPM is usually unilateral pleural effusion [81]. Occasionally, MPM can present as a pleural mass or with DPT with involvement of the interlobar fissures in the absence of pleural effusion. Pleural plaques, which are the witnesses of asbestos exposure, may be observed on chest X-ray. In later stages of the disease, an ipsilateral mediastinal shift may be seen secondary to encompassment of the lung by a thick rind of tumor and resultant significant unilateral loss of lung volume [82]. Patients with advanced MPM may have radiographic findings of mediastinal widening due to direct tumor invasion or lymph node involvement, enlargement of the cardiac margins secondary to pericardial invasion with effusion, and evidence of rib destruction or soft tissue masses extending from the chest wall.

A chest CT scan is the key imaging modality used for MPM evaluation and follow-up. Preliminary removal of fluid improves the visualization of pleural abnormalities. Unilateral pleural effusion, nodular pleural thickening and interlobar fissure thickening are the most frequent features observed [83, 84]. It is not rare to see a contraction of the affected hemithorax with associated mediastinal shift, narrowed intercostal spaces and elevation of ipsilateral diaphragm [83]. However, the accuracy of the

CT scan is suboptimal for correctly appreciating the involvement of mediastinal lymph nodes, chest wall and diaphragm [83]. These issues may potentially be improved by using multidetector row CT with multiplanar reformatting capacity.

The use of MRI can improve the detection of tumor extension, especially to the chest wall and diaphragm, and better predicts the resectability of the tumor [83]. Positron-emission tomography (PET) can be used to distinguish benign from malignant pleural masses and to increase the detection of occult distant metastases [85–87]. Integrated CT-PET, providing a better spatial resolution than PET alone, seems to be a sensitive technique for MPM staging [88]. Additionally, recent findings suggest that PET or PET-CT can provide prognostic [87, 89] and predictive (early detection of chemotherapy efficacy) information [90–92].

Thoracentesis, Percutaneous Pleural Biopsy, Thoracoscopy. Effusions associated with MPM are usually exudative with a lymphocytic predominance. If thoracentesis can diagnose a malignant pleural effusion, it only seldom leads to a precise diagnosis of MPM [93]. Concerning percutaneous pleural biopsy, it generally brings back little of the tissue material, which remains essential to confirm the diagnosis of MPM. Consequently, the diagnostic yield of these techniques is poor [94]. Thus, an invasive approach such as a thoracoscopy is very often mandatory to obtain a diagnosis of certainty.

Thoracoscopy is indicated in any patient without precise histopathological diagnosis in whom clinical and laboratory findings raise suspicion of MPM [95]. MPM gross appearance is a firm, grayish tumor coalescing on the visceral and parietal pleural surfaces into discrete plaques and nodules. The lung can be completely covered with a thick ring of tumor. Adjacent structures are involved at an advanced stage, with invasion of the chest wall, pericardium, diaphragm and interlobar fissures. In most patients, nodules and masses are associated with parietal pleural thickening up to several millimeters.

Thoracoscopy allows performing large biopsies of the parietal (and visceral) pleura under visual control. Thus, with a diagnostic yield >90% in MPM patients [94, 95], thoracoscopy is regarded as the standard diagnostic procedure for MPM (fig. 2). However, recent studies showed that thoracoscopy is less efficient in diagnosing the histologic subtype of MPM [96, 97].

Histology. MPM is typically classified into 4 histologic subtypes: epithelioid, sarcomatoid, desmoplastic and biphasic [98]. The epithelioid variant is the most common, comprising 50–60% of all mesotheliomas. Sarcomatoid

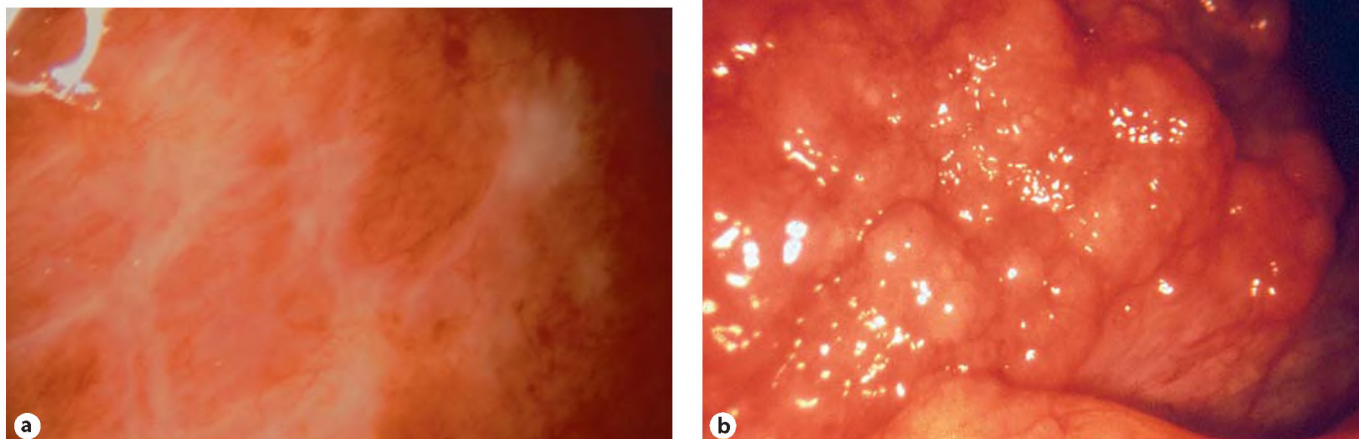


Fig. 2. Early- (a) and advanced-stage (b) malignant pleural mesothelioma. Endoscopic features are important prognostic parameters, in particular the invasion of visceral pleura and diaphragmatic muscle.

mesothelioma is composed of malignant spindled cells which may mimic malignant mesenchymal tumors such as fibrosarcoma or leiomyosarcomas. Biphasic or mixed mesothelioma has epithelioid and sarcomatoid features, and desmoplastic MPM is a rare variant of the disease.

Even with large pleural biopsies, histological diagnosis of MPM is difficult, because MPM can show various misleading histopathological pitfalls, and the pleura is a common site for metastatic disease. Visual similarities are particularly frequent between adenocarcinoma and epithelial MPM. Diagnostic problems also occur with benign inflammatory or reactive lesions of the pleura. These very frequent lesions occur often in patients of the same age group as MPM (pleural effusion during cardiac failure, collagen disease, pneumonia or cirrhosis). They may lead to atypical mesothelial hyperplasia which can result in diagnostic error [99].

Immunohistochemical staining of the biopsy tissue, using a panel of antibodies, is often necessary for the definitive diagnosis of MPM. Typically, MPM is characterized by the presence of staining for epithelial membrane antigen, calretinin, WT1, cytokeratin 5/6 and mesothelin, and the absence of staining for carcinoembryonic antigen, as well as the tumor glycoproteins B72.3, MOC-31 and Ber-EP4 and the epithelial glycoprotein BG8 [100].

Diagnostic Biomarkers. Because the diagnostic procedure of MPM is particularly hard, it is not rare that several months separate the first signs of the disease and the diagnosis of MPM [101]. Thus, it would be helpful to have

methods to speed up the diagnosis process and identify patients who require invasive procedures at an early time. The ideal diagnostic biomarker for MPM should be assessable using a blood or a pleural fluid sample and should be able to detect high-risk subjects developing the disease, to differentiate MPM from benign pleural diseases and metastatic pleural malignancies, and to reflect the disease severity or the tumor load.

Many candidate biomarkers have been studied for MPM, notably hyaluronic acid [102–104], Cyfra 21.1 [103, 105], carcinoembryonic antigen [103, 105, 106] and CA15-3 [105]. However, none were accurate enough to be used in clinical practice. Recently, new diagnostic biomarkers were proposed in serum, plasma and/or pleural fluid, notably soluble mesothelin-related peptides (or C-Erc mesothelin) [107–111], N-Erc mesothelin [112, 113] and osteopontin [114, 115]. In addition, global gene profiling using microarray technologies was used in tumor samples [116] and in pleural fluid [117, 118] to differentiate MPM from other diagnoses. These recent findings sound very promising, but the validation of diagnostic biomarkers in large and independent samples of patients remains a major challenge before their use in clinical practice.

Staging and Prognosis

MPM usually has a poor prognosis, with a median overall survival ranging from 4 to 12 months without treatment [71, 119]. In 1995, the International Mesothelioma Interest Group developed a new staging system for

MPM [120] (table 1). Although their staging system parallels prognosis, it is difficult to use it in daily practice, because it is based on surgical findings [120].

In a large retrospective series of phase II trials, the European Organization for Research and Treatment of Cancer (EORTC) found important prognostic factors: histological subtype, certainty of histologic diagnosis, performance status, white blood cell count and gender [121]. The Cancer and Leukemia Group B reviewed 337 patients treated for MPM and found that pleural involvement, lactate dehydrogenase >500 IU/l, poor performance status, chest pain, platelet count >400,000/ml, non-epithelial histology and increasing age >75 years jointly predicted poor survival [122]. Both EORTC and the Cancer and Leukemia Group B prognosis scores were validated in independent sets of patients [123, 124]. Recently, Bottomley et al. [125] demonstrated that some items of the EORTC-QLQ-C30/Lung Cancer 13 questionnaire were correlated with patient survival. Additionally, a very large number of biomarkers were assessed in a prognostic intent [110, 115, 126–130], but have not been validated in large and independent samples of patients at the present time.

Treatment

In the past decade, there have been several major developments in the management of MPM, especially thanks to the emergence of new therapies.

Chemotherapy. Until recently, chemotherapy for MPM was only assessed in small non-comparative phase II studies. With low median survival and objective response rates ranging from 10 to 26% for monotherapy [131–133], MPM was considered to be widely chemoresistant. A meta-analysis, using a systematic review of the literature including 88 studies, was published in 2002 and showed cisplatin as the most active single drug [134]. Due to the lack of efficacy of single agents, several combination regimens have been studied, with best results for combinations including antifolates and platinum compounds.

To date, only 2 phase III randomized trials have been published in the setting of first-line chemotherapy for MPM. First, Vogelzang et al. [135] randomized 222 MPM patients to cisplatin alone and 226 patients to a combination of pemetrexed and cisplatin. Pemetrexed is a multi-target antifolate agent that acts by blocking 4 different enzymes involved in folate metabolism and essential for cell replication (glycinamide ribonucleotide formyltransferase, thymidylate synthase, dihydrofolate reductase and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase) [136]. Combination therapy was associated with an improved response rate (41.3 vs. 16.7%;

$p < 0.001$) and a significantly better median survival (12.1 vs. 9.3 months; $p = 0.02$) and 1-year survival rate (50.3 vs. 38.0%; $p = 0.012$) compared with cisplatin alone [135]. In 2005, the results of a second phase III trial were published [137]. This trial, conducted by the EORTC Lung Cancer Group and the National Cancer Institute of Canada, compared a chemotherapy doublet with cisplatin and raltitrexed, another inhibitor of the antifolate pathway, with a monotherapy with cisplatin. The combination arm compared with the monotherapy arm showed a response rate of 23.6 versus 13.6% ($p = 0.056$), an overall median survival of 11.4 months (95% confidence interval, 10.1–15) versus 8.8 months (95% confidence interval, 7.8–10.8) and a 1-year survival rate of 46.2 versus 39.6% ($p = 0.048$) [137].

Taken together, these results led to the combination of cisplatin and an antifolate (pemetrexed or raltitrexed) as the standard therapy for MPM patients. As suggested by a phase II study [138], cisplatin could be replaced by carboplatin in the case of a contraindication to cisplatin. To answer the question of whether chemotherapy should be given immediately after diagnosis or whether there is time to wait, O'Brien et al. [139] compared freedom from symptom progression and overall survival in MPM patients with no or stable symptoms who received early chemotherapy (mitomycin C, vinblastine, and cisplatin [or carboplatin]) or late chemotherapy. Median time to symptom progression was longer with early compared with late chemotherapy (25 vs. 11 weeks; $p = 0.1$) [139]. Although not statistically significant, these findings support the use of early chemotherapy immediately after diagnosis of MPM.

After failure of first-line chemotherapy, no standard treatment has been defined. Few data are available in the literature concerning second-line chemotherapy. In a retrospective analysis of patients enrolled in the phase III trial of cisplatin plus pemetrexed versus cisplatin alone, Manegold et al. [140] observed a significantly prolonged survival in the groups treated with post-study chemotherapy (PSC). However, as PSC was not randomized, it is not possible to know whether the reduced risk of death was associated with PSC or whether patients who had prolonged survival tended to receive more PSC. In addition, some phase II trials on second-line chemotherapy have recently been published [141–143], with sometimes conflicting results [144, 145] (table 2). Thus, no standard treatment can be defined after failure of first-line chemotherapy.

Radiotherapy. Radiotherapy with an attempt to treat the entire involved pleural surface is technically difficult

Table 1. Staging system for MPM developed by the International Mesothelioma Interest Group**a** Tumor descriptions

Descriptor	Characteristics
<i>Primary tumor</i>	
T1a	Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura
T1b	Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci of the tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with a least 1 of the following features: Involvement of diaphragmatic muscle Confluent visceral pleural tumor (including the fissures) or extension of the tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Locally advanced but potentially resectable tumor; the tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with a least 1 of the following features: Involvement of the endothoracic fascia Extension into the mediastinal fat Solitary, completely resectable focus of the tumor extending into the soft tissues of the chest wall Nontransmural involvement of the pericardium
T4	Locally advanced technically unresectable tumor; the tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least 1 of the following features: Diffuse extension or multifocal masses of the tumor in the chest wall, with or without associated rib destruction Direct transdiaphragmatic extension of the tumor to the peritoneum Direct extension of the tumor to the contralateral pleura Direct extension of the tumor to one or more mediastinal organs Direct extension of the tumor into the spine Tumor extending through to the internal surface of the pericardium with or without a pericardial effusion, or the tumor involving the myocardium
<i>Lymph nodes</i>	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral, or contralateral supraclavicular lymph nodes
<i>Metastases</i>	
MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

b Staging

Stage	Tumor	Node	Metastasis
Ia	T1a	N0	M0
Ib	T1b	N0	M0
II	T2	N0	M0
III	Any T3	Any N1 or N2	M0
IV	Any T4	Any N3	Any M1

Table 2. Phase II studies assessing second-line chemotherapy for MPM

Regimen	Patients, n	RR, %	mTTP, days	mOS, days	Ref.
ZD0473	47	0	77	203	141
IPM	13 ^a	30	222	222	142
Pemetrexed	28 ^b	21	147	294	143
Pemetrexed + carboplatin	11	18	222	258	143
Raltitrexed + oxaliplatin	15 ^a	20	189	308	144
Raltitrexed + oxaliplatin	14	0	56	98	145

^a Subgroup of patients receiving the regimen as a second-line chemotherapy.

^b Twenty-five patients received pemetrexed as second-line and 3 patients as third-line chemotherapy.

RR = Response rate; mTTP = median time to progression; mOS = median overall survival; Ref. = reference; IPM = irinotecan + cisplatin + mitomycin C.

and associated with a high risk of radiation pneumonitis, myelitis, hepatitis and myocarditis [146]. When used alone, radiotherapy appeared to be ineffective in prolonging survival in MPM patients [146–148]. On the other hand, radiotherapy can be performed to palliate symptoms, especially to control pain [146, 149]. However, the duration of response, if there is one, is often short [149]. Prophylactic local radiation therapy to prevent parietal seeding after diagnostic examinations (thoracentesis, thoracoscopy, chest tube drainage) was demonstrated to be effective [150]. It is recommended to apply 21 Gy (in 3 sessions of 7 Gy for 3 days) to the sites of previous pleural drainage or punctures [151, 152].

Radiotherapy may be useful in combination with other treatments. After surgical resection, high-dose hemithoracic radiation therapy is a feasible treatment regimen and could improve local control [153]. Intensity-modulated radiotherapy might have even better results, because of its potential to conform doses more tightly to target volumes than conformal radiotherapy [154, 155].

Surgery and Multimodal Therapy. There are 3 sorts of surgery for MPM management: parietal pleurectomy, pleurectomy/decortication (P/D) and extrapleural pneumonectomy (EPP). Parietal pleurectomy involves removal of the whole parietal, diaphragmatic and mediastinal pleura, but this resection is very often incomplete [156]. Except in the early stage of the disease (Ia), parietal pleurectomy is a palliative procedure.

P/D associates pleurectomy with visceral decortication and entails resection of involved visceral pleural surface with preservation of lung parenchyma. P/D has a low surgical mortality rate (<5%) but is associated with a significant risk of local recurrences [157]. Moreover, this technique alone has not been shown to prolong survival.

That is the reason why some authors proposed its use in combination with various other therapies [158–162].

EPP includes the ‘en-block’ removal of the pleura, pericardium, diaphragm and the whole lung involved with the tumor. Consequently, macroscopic complete resection of MPM can be achieved more often with EPP than with P/D in selected patients [163]. However, this radical surgical procedure is associated with significant morbidity and with a mortality rate ranging from 3.4% [164] to more than 10% [165]. EPP is typically a part of multimodal treatment, including pre- or postoperative chemotherapy and adjuvant radiotherapy of the hemithorax [166–171].

Whether P/D or EPP is the best surgical approach for selected MPM patients is debated [163]. Indeed, these 2 techniques have never been compared in a randomized setting. Moreover, even if phase II studies reported promising results (median survival ranging from 13 to 26 months), there is to date no scientific evidence that multimodal treatment, including surgery, provides longer survival than chemotherapy alone. This question is addressed by an ongoing phase III study, the MARS trial [172].

Palliative Treatments. The most common and bothersome symptom of patients with MPM is dyspnea [94]. In the majority of cases, dyspnea is in relation with pleural effusion, which is usually recurrent. Talc pleurodesis by thoracoscopy (talc poudrage) is the method of choice for the management of recurrent pleural effusion in MPM patients [152, 173, 174]. Pleurodesis using talc slurry [175] or insertion of a chronic indwelling pleural catheter [176–179] are alternative options, especially for patients with a poor performance status or a limited life expectancy [152, 174].

MPM is often associated with pain, which is initially due to excessive nociception [152, 180]. Much later in the disease process, neurogenic pain (neuropathological) may arise due to invasion of nervous structures or as a side effect of therapy [152, 180]. Pain related to MPM should be managed as cancer pain in general, especially with opiates, non-steroidal anti-inflammatory drugs and anticonvulsants for the neurogenic part of the pain. Pain related to MPM can be controlled in around 90% of cases by oral treatments [152, 180]. However, neurosurgical techniques can be performed, but decisions should be taken solely by a multidisciplinary team experienced in pain management in general and in these techniques in particular and after careful evaluation of the benefit/risk ratio for each indication [152, 180].

Psychological and emotional factors are important in the palliation of MPM symptoms and should be managed attentively [181].

Future Directions. The use of agents that specifically target the biochemical and molecular changes underlying tumorigenesis could facilitate the combination of therapies to treat cancer on multiple fronts, offering the potential to significantly enhance tumor responses and improve survival. At present, several targeted therapies are under evaluation for MPM. Inhibition of angiogenesis is probably the most studied pathway. At least 5 anti-angiogenesis inhibitors, bevacizumab, semaxanib, sunitinib, pazopanib and thalidomide, have been or are used in clinical trials for the treatment of MPM. However, first reports did not show major improvement in outcomes [182, 183].

Several other pathways are suspected to play an important role in MPM pathogenesis. Platelet-derived growth factor is explored as a potential target for MPM treatment, particularly with ongoing studies using imatinib mesylate and dasatinib. The apoptotic pathway is also targeted by several new agents, such as bortezomib (a proteasome inhibitor that is under evaluation in com-

bination with cisplatin in a phase II EORTC study) [184, 185], and TRAIL agonists [186]. Mesothelin, a cell surface glycoprotein, is another attractive candidate for targeted cancer therapy given its limited expression on normal mesothelial cells and its high expression in several human cancers including mesothelioma, ovarian and pancreatic cancer [107]. The results of a phase I study with recombinant anti-mesothelin immunotoxin, SSP-1, were reported at the last ASCO meeting [187], and a phase II study is now ongoing. At last, the deacetylase inhibitor suberoylanilide hydroxamic acid (or vorinostat), which demonstrated some activity in phase I study [188, 189], is now assessed as single agent in second-line treatment and in combination with standard frontline chemotherapy.

Conclusion

As long as the use of asbestos is not regulated on a worldwide scale, asbestos-related pleural diseases will continue to affect populations. Benign asbestos-related pleural diseases are now well known and generally do not require specific treatments. Conversely, MPM is a poor prognosis disease with increasing incidence in many countries. In the last decade, some therapeutic progress has been obtained with the use of cisplatin combined with an antifolate. Moreover, several additional drugs or strategies provided preliminary promising results and are now under evaluation. However, research efforts for MPM must continue in numerous ways. Indeed, the early detection of MPM patients among asbestos-exposed subjects remains a real challenge. Moreover, tools for selecting MPM patients who will benefit from a specific therapy are needed. At last, an improvement in the knowledge of the molecular alterations that are specific to MPM is necessary to allow further development and testing of novel targeted agents in this disease in the future.

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