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Clinical Presentation and Natural History of Mesothelioma: Pleural and Pericardial

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This chapter reviews the clinical features of two types of malignant mesothelioma—pleural and pericardial. Although such distinction refers to the cavity of origin of this neoplasm, it is well known that each of these can spread to the other cavity when tumor progression occurs. In a total of 1496 cases of mesotheliomas reviewed pathologically, Suzuki (1) found the primary site to be pleural in 73.1%, peritoneal in 23.7%, and pericardial in 0.3%. The remainder (2.9%) had multicavitary involvement.

Malignant Pleural Mesothelioma

Clinical Presentation

Demographics and General Characteristics

There is uniformly a preponderance of males in all clinical series (Table 24.1) (2–8). This could be related to more common exposure to asbestos, the most important etiologic factor, in males. Men account for 68% to 79% of all cases of pleural mesotheliomas.

Mean and median age at diagnosis are usually between 54 and 59 years, with a very wide range. In fact, pleural mesothelioma can occur at any age, even in children. In a review of 80 cases of malignant mesothelioma in children, mean age was 9.7 years and 59% were boys (9). History of possible asbestos exposure was noted in two children. In addition, one patient had received radiotherapy for Wilms' tumor, and another one had a history of exposure to isoniazid in utero.

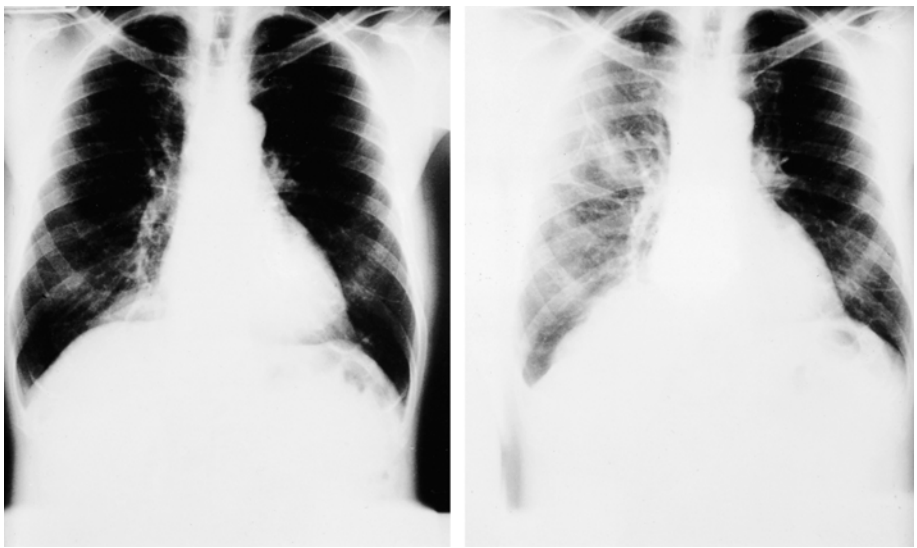
For pleural mesothelioma, the right side is more commonly involved, accounting for about 55% to 65% of cases. This could probably be explained by the preferential inhalation of asbestos fibers in the right lung.

Clinical Symptoms and Diagnosis

Typically the onset of symptoms is gradual and insidious (Fig. 24.1). Since the most common initial manifestation of pleural mesothelioma

Table 24.1 Clinical characteristics of patients with pleural mesothelioma

First Author (Reference) Year No. of Cases	Ratzer (7) 1967 $n = 31$	Chahinian (3) 1982 $n = 57$	Brenner (6) 1982 $n = 123$	Adams (4) 1986 $n = 92$	Ruffie (8) 1989 $n = 332$
Age (years)					
Mean/median	Med. 54	Mean 58	Med. 56	Mean 59	Mean 59
Range	13–70	24–75	5–77	28–80	22–88
Sex M (%)/F (%)	68/32	78/22	68/32	77/23	79/21
Initial symptoms (%)					
Dyspnea	6	37	29	59	29
Chest pain	71	33	37	69	33
Both dyspnea and pain	19	26			28
Cough	13	16	24	27	3
Hemoptysis	6	0			1
Hoarseness		0		3	1
Dysphagia		0			1
Weight loss		14		24	29
Fever		9		33	3
Asymptomatic (%)		4	4		3
Pleural effusion (%)	74	95		79	84
right (%)/left (%)	65/45	66/34	58/42		55/42
Symptoms to diagnosis					
Median		2 mos	3 mos		3.5 mos
Range		0–50 mos	0.5–24 mos		
Delay >6 months (%)		25			28



A B

Figure 24.1. This former asbestos worker was followed by routine periodic chest x-rays. A: A normal x-ray in April 1977. B: Minimal changes on the right side of the diaphragm and blunting of the right costophrenic angle in January 1979. These were the initial signs of pleural mesothelioma.

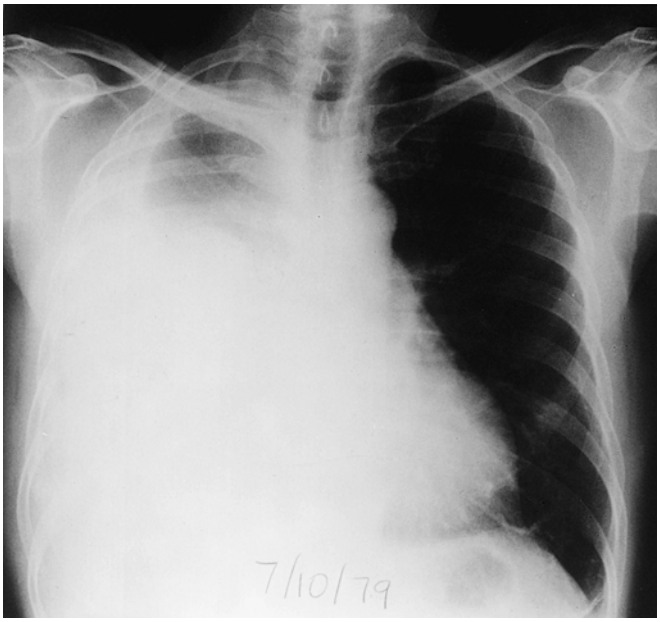


Figure 24.2. Chest x-ray of the same patient as in Figure 24.1 at presentation in July 1979. Massive right pleural effusion. Pleural biopsy showed malignant epithelial mesothelioma.

is a pleural effusion (Fig. 24.2), symptoms are dominated by dyspnea or chest pain. Initial symptoms in representative series are shown in Table 24.1. In our own experience based on 57 patients with pleural mesothelioma, initial symptoms were dyspnea (37%), chest pain (33%), both dyspnea and chest pain (26%), cough (16%), weight loss (14%), and fever without infection (9%) (3). The disease was discovered by routine chest x-ray in only 4% of patients. At this early stage, the degree of dyspnea is often related to the amount of pleural effusion, which occurs in up to 95% of patients (2,3). Chest pain is of the pleuritic type only in 10% of patients (4). More often, it is a steady pain localized to the involved hemithorax. The intensity of the pain is variable, from a dull twinge to a severe ache (7). Fever can be accompanied by night sweats and lead to an erroneous diagnosis of infection, particularly tuberculosis. Other presenting symptoms include, rarely, hemoptysis, dysphagia, Horner's syndrome, and hoarseness (8). Rare acute presentation can occur in less than 10% of patients and are due to spontaneous pneumothorax or acute hemothorax (8).

The presentation of pleural mesothelioma can be particularly challenging in young patients, where the index of suspicion is very low. We previously reported our experience with mesothelioma in young adults (age <40 years). Ten cases were seen at the Mount Sinai Hospital in New York between 1974 and 1987 out of a total of 181 patients with mesothelioma (10); six were pleural and four peritoneal, and age ranged from 24 to 39 years. Seven cases had a history of asbestos exposure, including five by household exposure, usually through the father. The median

latency period between first exposure and diagnosis was 19 years (range 13–34 years). Diagnosis was not suspected in most cases, and the median delay in diagnosis was 5.5 months. The presenting symptoms were diverse and included pain or dyspnea, malaise, cough, and fever. Pain was located at various sites, including any area of the thorax, but also the back or subscapular area. It is therefore important for the clinician to be aware of the possibility of this diagnosis even in young individuals or in children.

Physical findings are almost completely limited to those of a pleural effusion (11). Horner's syndrome is uncommon at this stage. Clubbing is also rare and was reported in about 6% of patients (2). Cardiac abnormalities on initial examination include a pericardial rub (2/57 patients), pericardial knock (1/57 patients), and a murmur of pulmonic stenosis (1/57 patients) (3). Electrocardiographic changes included right bundle branch block (5/57 patients), sinus tachycardia (3/57 patients), nonspecific ST-T changes (3/57 patients), atrial flutter (1/57 patients), and left anterior hemiblock (1/57 patients) (3). The possibility of early pericardial involvement should be considered and evaluated in such cases.

The median interval between first symptom and diagnosis is 2 months, but in our series 25% of patients had symptoms more than 6 months before diagnosis was made (3). Results of radiologic investigations are described elsewhere. Thoracentesis yields a serous to bloody fluid with the characteristics of an exudate (12). Pleural fluid glucose concentration can be low (12), while high levels of hyaluronic acid are highly suggestive of mesothelioma (13). Cytologic diagnosis is difficult. It shows malignant cells in about 35% of cases, but the diagnosis of mesothelioma is made in 10% or less (8,14). Percutaneous pleural needle biopsy can yield the diagnosis in about one third of cases (8). The cytologic and pathologic characteristics of mesothelioma are described elsewhere. Mesothelioma is an important cause of "idiopathic" pleural effusion. In 51 patients with pleural effusion of indeterminate etiology seen at the Mayo Clinic, four were subsequently diagnosed to have malignant mesothelioma (15). When the suspicion of mesothelioma is high enough based on the clinical and radiographic signs, and especially if a history of asbestos exposure is obtained, invasive procedures to obtain a final diagnosis are necessary and include thoracoscopy or thoracotomy.

There is a lack of positive serum markers currently available for the diagnosis of mesothelioma. Serum carcinoembryonic antigen (CEA) is usually within normal limits and is an important marker to distinguish adenocarcinoma from mesothelioma (2). On the other hand, an elevated serum level of hyaluronic acid may prove useful in differentiating mesothelioma from other tumors, or to follow the effect of treatment (2). The levels of CA-125 can also be elevated in mesothelioma. CA-125 is expressed in the nonneoplastic mesothelium and has been detected in 63% of malignant mesothelioma cells by immunohistochemistry, without a clear-cut correlation with serum levels (16). In 32 patients with malignant mesothelioma, we found an elevated serum level of CA-125 (<35 U/mL) in 44% (median 152 U/mL, range 47.6 to 1441 U/mL) (17). Serum levels of CA-125 were more often elevated in

cases of sarcomatous or mixed types (67%) as opposed to epithelial type (35%). Elevated levels were observed both in men (46%) and women (37.5%).

Paraneoplastic Syndromes

The most common paraneoplastic syndrome in pleural mesothelioma is thrombocytosis. We first reported this association in 1982 (3). Thrombocytosis (as defined by a platelet count above 400,000 per microliter) was seen in about 40% of patients at diagnosis and in up to 90% of patients during the course of the disease, a finding that has been confirmed by others (8,16). In addition, thrombocytosis has been linked to a poor prognosis (8,19). It has been suggested in a case of peritoneal mesothelioma that thrombocytosis was secondary to the large amounts of interleukin-6 (IL-6) produced by tumor cells (20), and this was confirmed in 25 patients with pleural mesothelioma (21). We found that serum levels of IL-6, as well as reactive proteins (C-reactive protein, α_1-acid glycoprotein, and fibrinogen) to be significantly higher in mesothelioma patients than in those with adenocarcinoma of the lung (21). There was a correlation between platelet count and serum IL-6 level. Levels of IL-6 in the pleural fluid of mesothelioma patients were even markedly higher than serum levels. In contrast, both serum and pleural fluid levels of tumor necrosis factor-α (TNF-α) were low in mesothelioma patients.

A full leukemoid reaction is much less common. Other hematologic manifestations include clotting abnormalities (venous thrombosis, pulmonary emboli) not necessarily associated with thrombocytosis, as well as disseminated intravascular coagulation and autoimmune hemolytic anemias (2,8). Rare associations with mesothelioma include the syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypoglycemia, and hypercalcemia (2,8). Hyponatremia has been reported in as many as 62% of patients with pleural mesothelioma, but its degree was minimal (mean ± standard deviation = 138 ± 5.4 mmol/L). It was hypothesized that rather than being secondary to ectopic secretion of ADH, it was due to ADH hypersecretion through a vagal reflex, either from involvement of pulmonary baroreceptors or by direct vagal stimulation by tumor (22). Parathyroid hormone–like peptide has been identified in mesothelioma cells, as well as in normal and reactive mesothelial cells (2).

Clinical associations that have been observed in patients with mesothelioma include various immunoproliferative disorders, particularly of B-cell origin (2,23). They include multiple myeloma, plasmacytoma, lymphocytic lymphoma, and chronic lymphocytic leukemia. A case-control study showed an association between occupational exposure to asbestos and large-cell lymphomas of the gastrointestinal tract and oral cavity (24). These observations provide further significance to immunologic abnormalities related to asbestos exposure and mesothelioma. Clinical observations also strongly suggest a genetic susceptibility to mesothelioma. Clusters of cases have been reported in some families, often by household exposure to asbestos, and also in identical twins (2). Similar observations were made after exposure to

erionite in Turkish villages (25). The growing knowledge of the genetic changes associated with mesothelioma will better explain these observations and shed more light on the pathogenesis of the disease.

Differential Diagnosis

Benign mesotheliomas are solitary fibrous tumors of pleura and are usually not related to asbestos exposure. These tumors of the visceral or parietal pleura are often pedunculated, and pleural effusion is exceptional. Most are benign, although a malignant form does rarely occur. Paraneoplastic syndromes that have been observed include clubbing and osteoarthropathy seen in up to 20% to 50% of cases, hyponatremia attributed to SIADH, and hypoglycemia (2).

A very difficult differential is related to the so-called benign asbestos pleurisy, which occurs in about 3% to 5% of asbestos workers (2). Its latency period from first exposure to asbestos is usually less than 20 years, making it the earliest abnormality, compared with other asbestos-related pleural diseases, such as mesothelioma, pleural plaques, and pleural calcifications. Confusion with malignant mesothelioma is common in view of a history of asbestos exposure and a bloody pleural fluid in the majority of cases. In contrast with malignant mesothelioma, however, the pleural effusion resolves spontaneously, but ipsilateral relapses are frequent and contralateral disease may appear. Pleural biopsy shows dense fibrosis with scattered nonmalignant cells. Close follow-up is necessary, since some patients have developed malignant mesothelioma 6 to 12 years after such an episode.

It is also difficult to distinguish malignant mesothelioma from metastatic carcinomas and sarcomas. Confusion with a peripheral adenocarcinoma of the lung metastatic to the pleura is frequent, not only on frozen sections but also on fixed paraffin sections. The pathologic differential diagnosis is discussed elsewhere. Recognizing mesothelioma as the cause of a malignant pleural effusion is important in order to avoid a time-consuming, fruitless, and expensive workup in search of another primary site.

Natural History

The natural history of pleural mesothelioma is of relentless growth in the hemithorax with early involvement of surrounding structures including lung, diaphragm, chest wall, pericardium, mediastinum, and direct spread to the peritoneum and contralateral hemithorax (Fig. 24.3) (2,3). Seeding within the track of needle biopsy or surgical incision is also common (Fig. 24.4). Gradual thickening of the involved visceral and parietal pleura leads to constriction of the hemithorax, and obliteration of the pleural space with decrease or disappearance of pleural effusion at that stage, leading to a "frozen" hemithorax. Characteristic symptoms are increasing pain and dyspnea. Cardiac findings are common at this stage and were reviewed in 64 patients with pleural mesothelioma at our institution (26). The electrocardiogram was abnormal in 89% of patients. Over half (60%) had an arrhythmia, including sinus tachycardia (42%), premature atrial or ventricular contractions (13%), atrial fibrillation

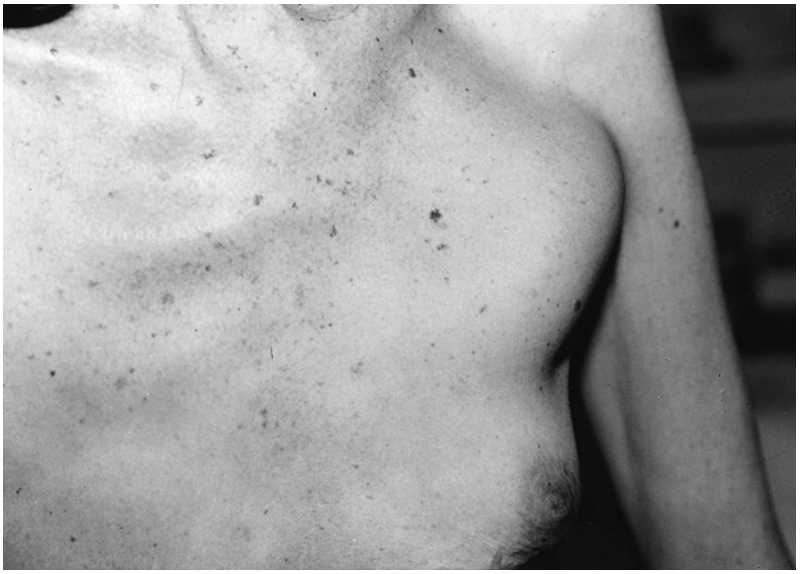


Figure 24.3. Massive chest wall involvement in a patient with pleural mesothelioma.

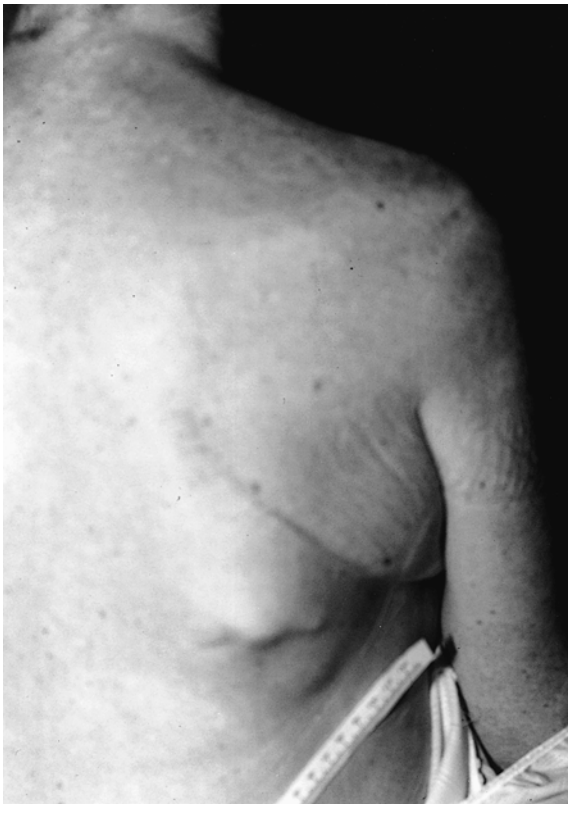


Figure 24.4. Seeding at the surgical scar of prior chest tube insertion in a patient with pleural mesothelioma.

(3%), and atrial flutter (1%). Over one third (37%) had a conduction abnormality, such as complete or incomplete right bundle branch block (27%), or left anterior or posterior hemiblock (8%). Low-voltage QRS was seen in 3% only, and no patient had a left bundle branch block.

Although the clinical picture remains dominated by the local disease, metastases are common and include possible lymphatic spread to mediastinal, cervical, axillary, retroperitoneal, and mesenteric lymph nodes, as well as hematogenous metastases to liver, spleen, adrenals, bone, gastrointestinal tract, pancreas, kidneys, uterus, bone marrow, and even brain (3,27). Such metastases are often found at autopsy, where only 20% of patients with pleural mesothelioma had disease limited to the thorax (2,3), but these metastases rarely contribute to death. It is noteworthy that at autopsy, cardiac invasion to pericardium, epicardium, and even myocardium was found in 74% of patients, most often by direct invasion, and thromboembolic events were noted in 28% (3,27). Two cases of calcified liver metastases have been reported (28,29). These calcifications were attributed to degenerative changes and necrosis of metastases.

In our experience, median survival was 17 months from first symptoms and 13 months from diagnosis, with a survival of 56% at 1 year and 22% at 2 years following diagnosis (3).

Malignant Pericardial Mesothelioma

Whereas pleural mesothelioma commonly spreads to the pericardium, primary pericardial mesothelioma is exceptional but has been well described. It was previously reported under various names including coelothelioma, endothelioma, and endothelial carcinoma (30). Like pleural mesothelioma, histologic types can be epithelial, sarcomatous, or mixed (30,31). Asbestos exposure has been reported, and in prospective studies was found to definite in three of 15 cases (20%) and possible in four of 15 (27%) (32). In further support of this association, asbestos bodies have been occasionally identified within pericardial mesothelioma (33).

Pericardial mesothelioma accounts for about half of all pericardial tumors (34,35). More than 80 cases were reported by 1967. Only a small fraction of patients (less than 20%) had been diagnosed antemortem. Since then progress in imaging and biopsy techniques have allowed definitive diagnosis at presentation. In a more recent review, a total of 28 cases were reported in the English literature from 1972 to 1992. The mean age was 47 years, asbestos exposure was documented in 14% and prognosis remained poor (31). There are over 200 cases reported worldwide (33). In the review by the Armed Forces Institute of Pathology (AFIP), Washington, DC, on 59 patients, the mean age was 46 years, ranging from 2 to 78 years. The male/female ratio was 2:1, somewhat lower than the ratio reported in pleural mesothelioma (33).

A variety of clinical symptoms have been observed, from those of pericardial effusion (often bloody) with dyspnea and pain, to those of constrictive pericarditis or vascular compression (superior vena caval

syndrome, constriction of great vessels) (34). Cardiac tamponade can be the revealing event, or can occur later, often as a terminal manifestation (36). Echocardiography reveals pericardial thickening or effusion, but a mass is detected in only 12% of patients (31). Computed tomography similarly reveals various degrees of pericardial thickening and fluid, and a mass is seen in 44% of cases (31). In addition, search for pleural involvement as well as signs of asbestos exposure (pleural plaques and calcifications) is important. Magnetic resonance imaging is most useful in assessing the disease and evaluating its extent (37). Effusion cytology revealed malignant cells in only 20% of cases (31).

Although pericardial mesothelioma can occasionally mimic tuberculous pericarditis, lupus erythematosus, rheumatic fever, or even cardiac myxoma (33), the major differential diagnosis includes metastatic tumors to the pericardium, by far more common and which can be seen in almost any type of carcinoma, leukemia, and lymphoma. It is often difficult to differentiate mesothelioma from metastatic adenocarcinoma, and special stains as well as electron microscopy are useful. Other primary malignant cardiac tumors, which are usually sarcomas (38), can also be difficult to distinguish from pericardial mesothelioma, especially in its sarcomatous form. Angiosarcoma is the most common primary cardiac malignant tumor and its gross aspect can mimic mesothelioma (33,38). Immunohistochemical stain for factor VIII–related antigen can be helpful, since it is usually positive in angiosarcoma (33). Finally a biphasic aspect (mixed epithelial and sarcomatous) is very characteristic of mesothelioma but two other tumors can present a similar histologic dichotomy, including synovial sarcoma and invasive thymoma (33). The diagnosis of these tumors require detailed gross and microscopic evaluation, which are beyond the scope of this chapter.

Mesothelioma of the atrioventricular node is very rare (about 50 cases reported), and usually is minute or even microscopic (2). Partial or complete nodal heart blocks and sudden death are the major consequences of this tumor. Two thirds occurred in females, and age ranged from an 8-month-old fetus to an 86-year-old woman. The natural history of pericardial mesothelioma, like its pleural counterpart, is of relentless growth. These tumors are usually diffuse, covering most of the heart, often obliterating the pericardial cavity, and may invade the myocardium and invade surrounding tissues (pleura, lung, mediastinal nodes). Distant metastases have also been seen occasionally (34,36).

Treatment is usually purely palliative, and 50% to 60% of patients are dead within 6 months (33,34). The prognosis of pericardial mesothelioma appears clearly worse than that of pleural or peritoneal mesotheliomas (AFIP). Only one patient was reported to be alive at 5 years, following treatment with partial surgical resection and radiation (35). Another patient survived 1 year after similar treatment.

Addendum

Since submission of this manuscript, another marker for mesothelioma has been identified. Mesothelin is a differentiation antigen originating from a precursor protein processed to a 40 kDa cell membrane-bound

protein and a soluble 31 kDa fragment also called megakaryocyte-potentiating factor (39–41). Mesothelin seems to be normally expressed only in mesothelial cells, and its biologic function is unknown, but it may have a role in cell adhesion. Interestingly it can bind to CA-125 (41). It does not seem to affect platelet production in humans. Elevated serum levels of soluble mesothelin have been reported in 37 (84%) of 44 patients with malignant mesothelioma, and in only 3 (2%) of patients with other cancers or inflammatory lung or pleural diseases (39). However elevated serum levels have also been found in other tumors including ovarian, pancreatic, and other carcinomas. The role of mesothelin as a therapeutic target merits further investigations.

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