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Diffuse malignant mesothelioma of the pleura: a clinicopathological study of six patients with a prolonged symptom-free interval or extended survival after biopsy and a review of the literature of long-term survival

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Abstract. Diffuse malignant mesothelioma of the pleura generally proceeds rapidly with clinical deterioration soon after the initial histopathological diagnosis of the tumor. We encountered six patients in whom the symptom-free interval after biopsy was surprisingly prolonged. Histopathologically, the tumor in each case was epithelioid with prominent myxoid stroma and formation of tubules and micropapillae. Cytologically, the malignant cells had relatively regular nuclei with bland chromatin. As individual findings, these histological and cytological features are common in diffuse malignant mesothelioma. However, the combination of (1) bland cytology of epithelioid cells, (2) formation of tubular and micropapillary patterns, (3) a myxoid stroma and (4) an absence of sclerosing desmoplasia, as observed in these six cases, might indicate indolent disease at the outset in a few patients. It is possible that these features are related to early stage of disease rather than having discriminatory value in their own right. We do not conclude that initially restrained disease necessarily presages a longer mean survival because the follow-up in these patients has not been long enough. We present these observations because, to date, this malignancy has proven so refractory to clinical management.

Key words: Mesothelioma – Pleura

Introduction

Diffuse malignant mesothelioma of the pleura is a malignancy which generally results in death after several months or a few years whether or not the patient is treated by surgery or chemotherapy (Antman 1980; Law et al. 1984; McCaughey et al. 1985; Chailleux et al. 1988). In view of the bleak outlook for these patients, any information assisting in prognosis might be useful. When patients do unexpectedly well, the accuracy of the diagnosis may be questioned and the pathology reviewed a second time.

We encountered six patients with pleural disease who were biopsied and proved to have a diffuse malignant mesothelioma. Each patient lived for an interval of 1 year or longer essentially free of symptoms. These six cases had histological features in common and comprise the body of this report. This is not a case control study in which the clinical and pathological features of these six patients are matched against other patients with diffuse malignant mesothelioma. It is, rather, a report of the histological features shared by these six cases.

Materials and methods

In the course of continual clinical and pathological study of approximately one thousand patients with tissue samples of diffuse malignant mesothelioma of the pleura or diseases which might be confused histologically with that tumor, we encountered six patients who had diffuse malignant mesothelioma with common histological features and who were either (1) alive and well with some form of treatment 3 years or more after initial histological diagnosis of malignancy, (2) alive and well without treatment 1 year after initial histological diagnosis of malignancy, or (3) dead from an unrelated cause and had only microscopic amounts of mesothelioma at autopsy. The biopsies of three patients had been seen in consultation by one of the authors (E.J.M.). The other three patients had been admitted to the Massachusetts General Hospital for diagnosis and treatment, and one of these patients (case 3) has been the subject of a Case Record (1990). The study was restricted to diffuse malignant mesothelioma of the pleura occurring in adults. We tabulated the clinical results from review of the patients' records and from clinical follow-up from attending physicians.

We reviewed the histological slides of the biopsies and of the two autopsies. All of the cases were subclassified as epithelial, biphasic or sarcomatoid as described by McCaughey et al. (1985). At least two slides were available from each case. Histochemical study for mucin was performed in five cases. Immunohistochemical study for carcinoembryonic antigen and keratin was performed in five cases in which paraffin-embedded tissue was available in order to exclude metastatic adenocarcinoma to the pleura.

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Results

The clinicopathological features of the six patients are summarized in Table 1. Four patients were male and two were female. Three were in their eighth or ninth decade of life. Four patients presented with dyspnea and two with pleuritic chest pain. One patient (case 2) had been diagnosed as having metastatic adenocarcinoma, but she was alive with no known primary tumor after 2 years. Chest radiographs disclosed pleural effusion or diffuse pleural thickening in all cases. No intrapulmonary mass was seen in any case after fluid had been removed. Three patients had needle biopsy of the pleura, two had open biopsy of the pleura, and one patient had a parietal pleurectomy after frozen section diagnosis of mesothelioma. A debulking procedure was performed in one patient at a later time. Three patients received chemotherapy at some time in their course. Two patients received radiotherapy to the chest. One patient received no treatment other than instillation of sclerosing agents to prevent accumulation of fluid. Five patients were alive and well with minimal or no symptoms at intervals of approximately 1, 2, 3, 4 and again 4 years, respectively, after initial histopathological diagnosis of mesothelioma. One of these five patients died of diffuse malignant mesothelioma and pulmonary fibrosis 5 years after initial diagnosis. One patient died of coronary artery disease, emphysema and bronchopneumonia 1 year after diagnosis. He had microscopic foci of mesothelioma in pleural adhesions and in subpleural adipose tissue of the chest wall at autopsy. These foci of superficial invasion did not contribute to his death. One patient (case 4) had concurrent mesothelioma in the peritoneal cavity. No patient proved to have a carcinoma in the lung or elsewhere in the body.

All four males in our study were exposed to asbestos in the course of their occupation. We do not have any occupational or environmental history of exposure to asbestos for the two female patients. No patient had received radiotherapy to the chest prior to the development of the pleural mesothelioma.

Macroscopically, tumor invaded deeply into the lung in the autopsy of one patient who died of tumor. The tumor in this case also formed distinctive myxoid nodules upon the pleura (Fig. 1).

Histopathologically, each case of diffuse malignant mesothelioma was epithelioid with some component of papillarity. In four cases, tumor at biopsy was confined to diffusely thickened parietal or visceral pleura (Fig. 2) and did not involve adjacent adipose tissue of the chest

Table 1. Clinicopathological features of the present cases

Patient	Age/sex	Symptoms (duration)	X-ray	Diagnostic procedure	Pathological extent of tumor	Histology	Treatment	Survival
1	78/M	Dyspnea	Pleural effusion	Pleural needle biopsy and autopsy	Tumor in thickened pleura	Tubular; myxoid stroma	Chemo-therapy	Died of unrelated cause (1 year)
2	75/F	Pleurisy	Pleural thickening	Pleural needle biopsy of tumor	Polypoid fragment	Tubulo-alveolar; edematous fibrous stroma	None	Alive (2 years)
3	42/F	Pleurisy (3 years)	Pleural thickening	Open biopsy of lung and pleura	Diffusely thickened visceral pleura; superficial invasion of lung	Tubulo-alveolar; edematous fibrous stroma	Chemo-therapy	Alive (3 years)
4	84/M	Dyspnea with chronic cough (2 months)	Pleural effusion	Pleural needle biopsy	Tumor creeping upon hyaline plaque	Tubulo-papillary; edematous fibrous stroma	Thora-centesis	Alive (1 year)
5	60/M	Dyspnea (2 months)	Pleural effusion	Open biopsy of lung and pleura	Diffusely thickened visceral pleura	Tubulo-papillary; myxoid stroma	Debulking of tumor and radio-therapy	Alive (4 years)
6	65/M	Dyspnea with chronic cough (12 months)	Pleural effusion	Parietal pleurectomy	Parietal pleura studded with pebbles	Tubulo-papillary; myxoid stroma	Chemo-therapy and radio-therapy	Died of tumor (5 years)

Fig. 1. Nodular deposition of myxoid tissue in major fissure of lung at autopsy (case 6)

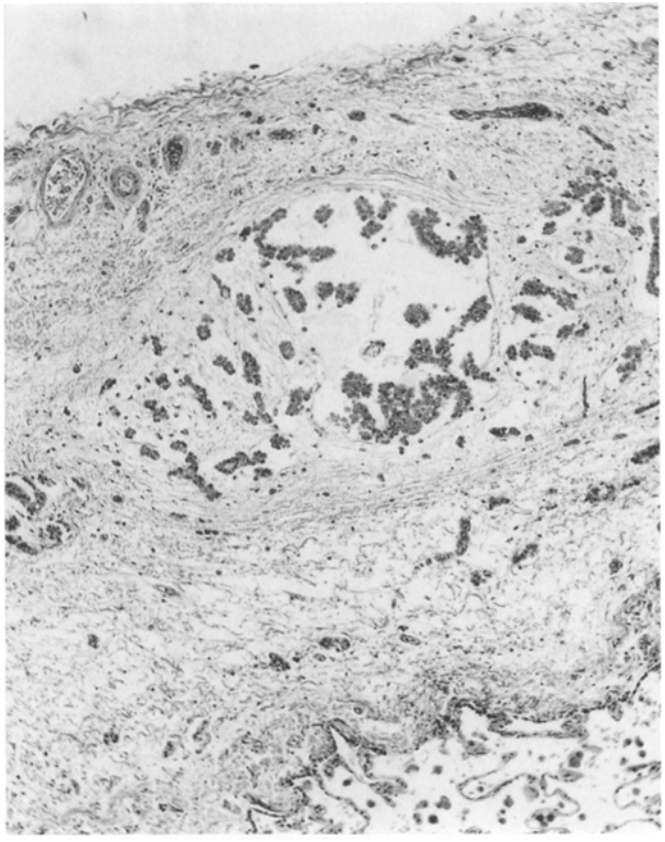

Fig. 2. Diffuse malignant mesothelioma in visceral pleura. Aggregated small nests of tumor lie in myxoid fibrous tissue with focal cystic degeneration. Lung (*bottom*) is not invaded by tumor (case 5, ×79)

wall or lung, respectively, except for invasion of contiguous interlobular septum (Fig. 3) and a few subpleural alveoli in one case. The tumor was in situ in one biopsy to the extent that malignant epithelioid cells formed micropapillae upon the serosal surface of a pleural hyaline plaque (Fig. 4). One biopsy consisted of a small polyp of mesothelioma (Fig. 5).

Malignant epithelioid cells formed long thin tubules. Some tubules were dilated into cysts a few millimeters in diameter. Cytologically, the malignant epithelioid cells were small with oval and slightly hyperchromatic nuclei and relatively abundant cytoplasm. Solid nests of proliferating atypical mesothelial cells embedded in fibrin were not a diagnostic feature of these cases. No anaplastic tumor was seen in any biopsy, resection specimen, or autopsy. Tubular tumor invaded adipose tissue of the chest wall (Fig. 6) at autopsy of one patient who died with tumor but not of tumor.

The thickening of the pleura was due in large part to proliferating myxoid fibrous tissue which surrounded the neoplastic tubules. The mesenchymal tissue appeared reactive and not neoplastic. The mesenchymal cells did not stain for keratin. The myxoid fibrous tissue differed from the neoplastic fibrous tissue formed in the desmoplastic variant of diffuse malignant mesothelioma by being loose and edematous rather than dense and sclerotic. The spindled nuclei which are wedged tightly between broad bundles of collagen in desmoplastic diffuse malignant mesothelioma were not present in these cases.

All of the malignant epithelioid cells stained for keratin. None stained for mucin with mucicarmine, with periodic acid-Schiff after digestion with diastase, or for carcinoembryonic antigen.

Discussion

Because diffuse malignant mesothelioma carries such an ominous prognosis, pathologists are generally conservative in initial diagnosis and clinicians are generally conservative in initial therapy (DaValle et al. 1986; Martini et al. 1987). More than 80% of patients have pleural effusions with or without dyspnea at the time of diagnosis (Klima et al. 1976; Legha and Muggia 1977; McCaughey et al. 1985; Martini et al. 1987; Rusch 1990). If dyspnea is present initially, it generally progresses over the following months except for temporary relief after removal of pleural fluid. Chest pain is a common presenting complaint that almost always appears at some time and often dominates the clinical problem. Some patients have a short symptom-free interval after biopsy diagnosis, but it is highly unusual for a patient

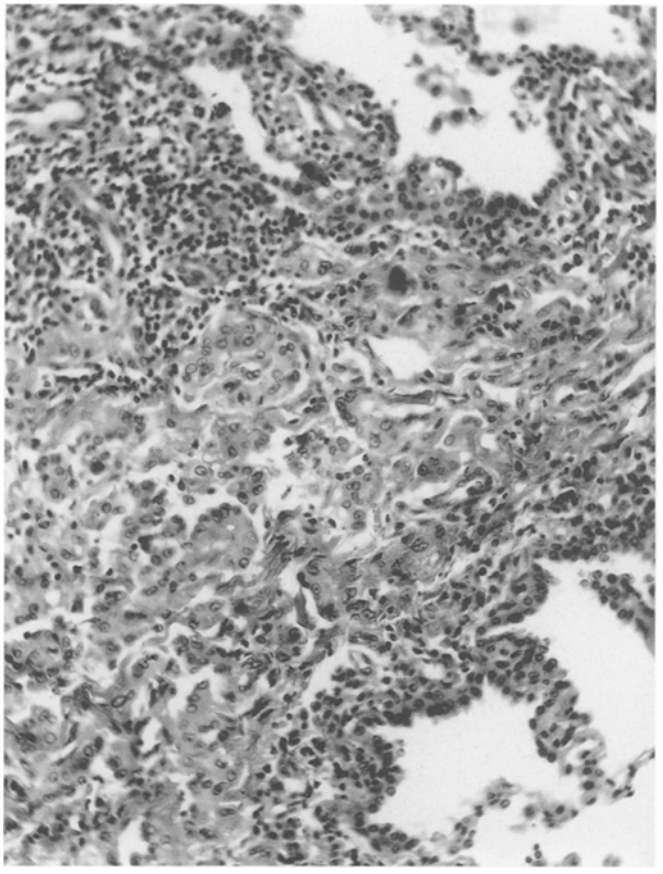

Fig. 3. Nests of diffuse malignant mesothelioma expanding an interlobular septum as tumor dissects from the interstitial layer of the visceral pleura (*left*) into lung parenchyma. Alveoli on both sides of septum (*top and bottom*) are free from tumor (case 3, × 200)

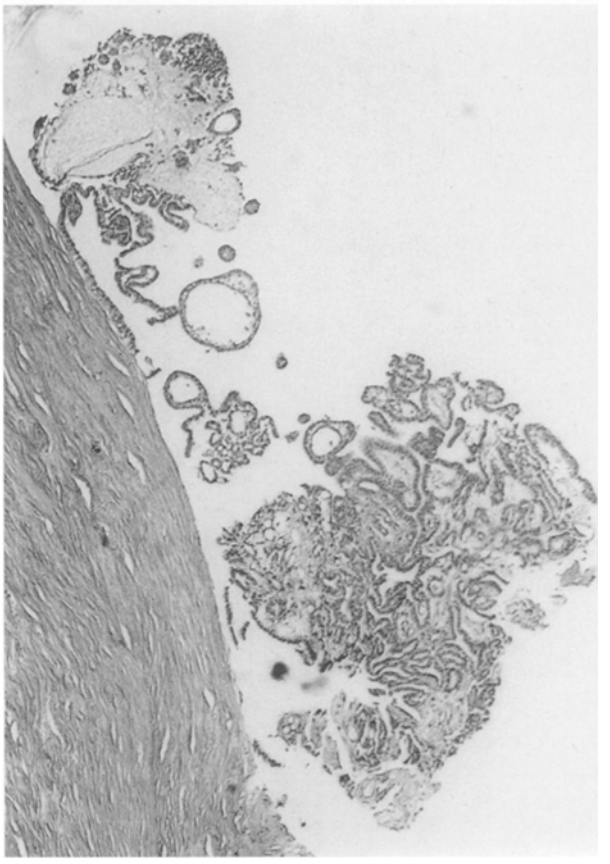

Fig. 4. Micropapillary diffuse malignant mesothelioma upon pleural hyaline plaque (*left*; case 4, × 60)

to be symptom-free for 1 year (Chahinian and Holland 1978; Colbert et al. 1985; Adams et al. 1986; Ruffie et al. 1989).

We were interested in whether a prolonged symptom-free interval or histological type of diffuse malignant mesothelioma predicts a survival better-than-average, based on the literature. Reports of survival of 5 or more years after initial histological diagnosis of diffuse malignant mesothelioma of the pleura (Porter and Cheek 1968; Oels et al. 1971; Worn 1974; Buchart et al. 1976; Klima et al. 1976; Wanebo et al. 1976; Fischbein et al. 1978; Antman 1980; Brenner et al. 1982; Chahinian et al. 1982; McCormack et al. 1982; Nauta et al. 1982; Martensson et al. 1984; Adams et al. 1986; DaValle et al. 1986; Harvey et al. 1990; Waltz and Koch 1990) are listed in Table 2. This table does not include patients whose reported interval of survival begins at the time of initial symptom. Although a review of the literature on initially subdued disease would be most applicable to this study, previous publications do not describe the magnitude of, or ascribe significance to, a prolonged symptom-free interval. The majority of reports that list or illustrate histology indicate an epithelial type of tumor. Some of these reports suggest that epithelial types of mesothelioma have a slightly better prognosis (Oels et al. 1971; Wanebo et al. 1976; McCormack et al. 1982; Nauta et al. 1982). One report stated that stage 1 examples of pure epithelial type carry a better prognosis, especially when the tumor consists entirely of abundant edematous mucoid stroma with loosely arranged tumor cells (Buchart et al. 1976). This is essentially in agreement with our experience. Other reports suggested that the desmoplastic and sarcomatous types metastasize more often and have a slightly worse prognosis (Kannerstein and Churg 1980; Cantin et al. 1982). Our cases all lacked desmoplastic and sarcomatous elements. Other reports could draw no conclusion between histology and prognosis for diffuse malignant mesothelioma of the pleura (Adams et al. 1986; Antman et al. 1988; Waltz and Koch 1990).

Clinical and pathological criteria for prognosis in general oncology rely on stage of disease (Rosenberg 1985). For some types of tumor, histology has independent discriminatory value (Lieberman and Lebovitz 1990). Since stage of tumor is important in most of oncology, there is no reason to believe that stage is not important in diffuse malignant mesothelioma of the pleura. However, it is uncommon to find, or to be able to prove, that diffuse malignant mesothelioma is confined to the parietal or visceral pleura, as distinguished from early

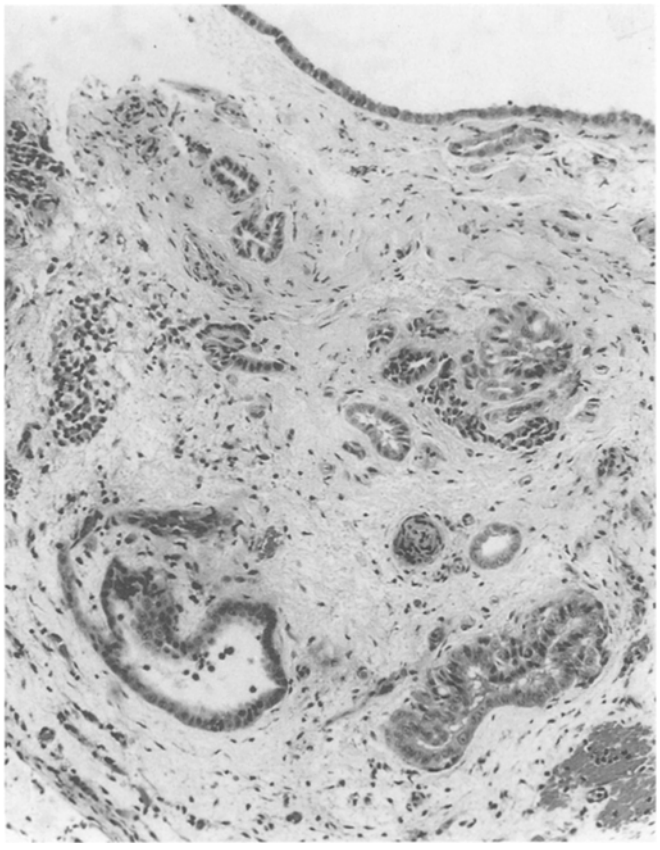

Fig. 5. Portion of a polypoid piece of diffuse malignant mesothelioma with wall of a microcyst (*top right*) and tubules in myxoid stroma (case 2, ×125)

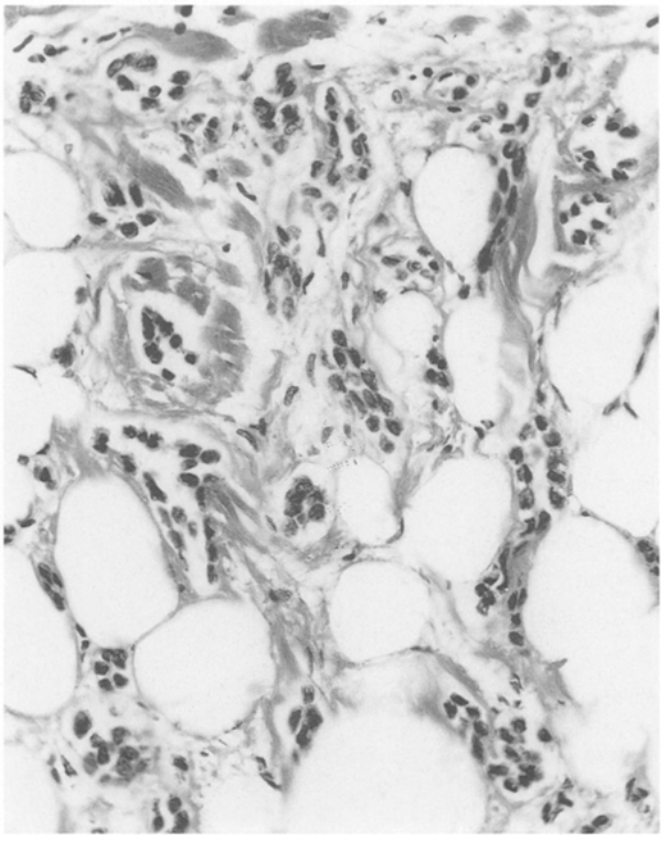

Fig. 6. Small tubules invading adipose tissue of the chest wall (case 1, ×313)

invasion of the chest wall or lung, even at initial presentation. The initial pathological diagnosis is usually suspected or made only on cytological examination of pleural fluid or on a small biopsy-sample. Pleural decortication specimens usually do not contain sufficient endothoracic fascia or lung to assess invasion. Early invasion of the lung can be evaluated completely only in those few patients who are treated with radical extrapleural pneumonectomy. A staging system for mesothelioma has been devised (Buchart et al. 1976), in which stage 1 disease is tumor confined to one hemithorax. A much earlier stage would be one where the diffuse malignant mesothelioma is confined to the visceral or parietal pleura and not present in lung or other structures in the hemithorax. Such localized disease (i.e., T status) would correspond to T1 in the TNM-based system (Rusch 1990). Only in this stage would pleural stripping have a chance to extirpate the tumor. Four of our cases might fit into this very early stage based on the best available pathological evidence, but we appreciate that two of the initial biopsies are tiny and by themselves not sufficient for pathological staging. Computerized axial tomography of the chest after removal of fluid would have been the best method to assess extent of the pleural disease but was not performed in these patients.

Well-differentiated diffuse malignant mesothelioma has been reported in the peritoneum as one histological form of mesothelial neoplasm with much less aggressive behavior than the standard peritoneal mesothelioma (Foyle et al. 1981; Burrig et al. 1990; Daya and McCaughey 1990). These neoplasms generally occur in women and may reflect special properties of the mesothelial cells that cover the ovary and line the female pelvic peritoneum. Diffuse malignant mesothelioma of the standard variety in women is related to asbestos, but well-differentiated papillary proliferations of the peritoneum of women are not so related and probably are a different disease. One case of localized, encapsulated, papillary mesothelial tumor in the thorax has been described (Yesner and Hurwitz 1953).

Atypical mesothelial proliferations associated with recurrent pleural effusions may be difficult to differentiate from diffuse malignant mesothelioma (Sheldon et al. 1981; Tuder 1986; Yokoi and Mark 1991). Our cases differed from five cases reported by Hansen et al. (1984) by having histological specimens available in addition to cytology in all cases, tumor grossly visible in four cases, and a stromal component surrounding glandular structures as well as forming cores of papillary structures. Solid nodules of atypical mesothelial cells, as may

Table 2. Previous reports of long-term survival (5 or more years) in diffuse malignant mesothelioma of pleura

Study	Year	Total number of patients	Patients surviving 5 years	Primary treatment	Stage	Histological type
Porter and Cheek	1968	7	1	Radiation		
Oels et al.	1971	28	1	Chemotherapy or radiation		
Worn	1974	248	10%	Pleural stripping or extrapleural pneumonectomy		
Wanebo et al.	1976	39 27	3 2	Pleural stripping Pleural stripping and radiation		Epithelial, fibrosarcomatous
Klima et al.	1976	12	2	Pleural stripping and radiation		Epithelial
Buchart et al.	1976	29	1	Pleural stripping		Epithelial with myxoid stroma
Fischbein et al.	1978	1	1	Biopsy		Epithelial
Antman	1980	10	1	Pleural stripping		
McCormack et al.	1982	7 63	1 2	Pleural stripping Pleural stripping and radiation		Fibrosarcomatous, epithelial
Chahinian et al.	1982	57	2	Chemotherapy and radiation		
Brenner et al.	1982	123	7	Pleural stripping	I:3/7, II:4/7	Epithelial 3/7, fibrosarcomatous 3/7, other 1/7
Nauta et al.	1982	32	1	Radiation and chemotherapy	I	Epithelial
Martensson et al.	1984	32	3	Pleuropneumonectomy and chemotherapy		Epithelial with papillary pattern
Adams et al.	1986	92	2	Chemotherapy or radiation		Epithelial
DaValle et al.	1986	33	2	Extrapleural pneumonectomy		Epithelial
Waltz and Koch	1990	64	4%	Biopsy or pleural stripping		Epithelial
Harvey et al.	1990	94	3	Extrapleural pneumonectomy		

be seen in nodular mesothelial hyperplasia in hernia sacs (Rosai and Dehner 1975) were not grounds for inclusion of cases into our study and not part of the histology in these cases.

Relatively innocuous nuclear features, sparsely distributed glands and tubules, micropapillae, and myxoid stroma are each commonly observed in patients with diffuse malignant mesothelioma who have the anticipated short survival with or without therapy. The diagnosis of a tumor with only these histological features and confined to the pleura may be difficult to establish initially on a small biopsy, and the diagnosis may be questioned by the attending physician when the patient is relatively asymptomatic. The combination of the histopathological features described here in a tumor confined to the pleura at the time of initial biopsy raises the possibility, albeit small, of a prolonged interval free from symptoms. We hasten to add that this does not necessarily mean an increase in the expected length of survival. We do not know whether these features are related to early stage of disease or are independent of stage.

Other cases of diffuse malignant mesothelioma that we reviewed had micropapillae, long thin tubules, myxoid fibrous tissue, or confinement to the pleura. Although we sought to establish histological criteria that might identify patients with the possibility of a prolonged interval free from major symptoms, this was not a case-control study to compare the six cases reported here against all other cases of diffuse malignant mesothelioma. However, the six cases described in this report had a commonality under the microscope.

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