CLINICAL REVIEW

Pleural Mesothelioma: Clinical Features and Therapeutic Implications

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A detailed review of the literature was done to define the epidemiology, pathology, clinical features, and treatment of pleural mesothelioma. It appears that pleural mesothelioma accounts for approximately 400 deaths each year in the United States. Asbestos has been definitely implicated in the etiology of this disease. The common clinical features include chest pain, pleural effusion, and radiologic findings of irregular pleural thickening or pleural densities. Therapeutic modalities used in the past have included surgery, radiation therapy, and, more recently, chemotherapy. A combined modality approach to treatment appears more promising.

FORTY-FIVE YEARS AGO, largely because of difficulties in diagnosis, there was little consensus supporting mesothelioma as a distinct disease entity. Because of wide variations in the appearance of the growth both grossly and microscopically, pleural tumors either were believed to arise in the chest wall and were variously named endotheliomas, pleural sarcomas, or endothelial carcinomas, or they were presumed to be metastases from primary tumors located elsewhere. In 1931, Klemperer and Rabin (1) advocated general use of the term mesothelioma for primary-pleural tumors originating from the surface lining cells or the mesothelium. The confirmation of the origin of mesothelioma came in 1942 from the tissue culture studies by Stout and Murray (2), who showed that mesothelial cells could differentiate into epithelial as well as mesenchymal elements. They also showed the ability of fibroblastic cells in mesotheliomas to transform into epithelial elements and vice versa.

In addition to their pleural origin, mesotheliomas of other serosal surfaces such as peritoneum pericardium and tunica vaginalis of the testis are well known. The pleural site is most frequently involved and accounts for 60% to 70% of all reported mesotheliomas, whereas peritoneal tumors occur in approximately one third of the cases (3-5). Pleural mesotheliomas are classified into the diffuse tumor type, which is present in about 75% of the cases, and solitary or localized tumors, which comprise the remaining 25% (Table 1). The highly malignant diffuse disease has a rapidly fatal course but the solitary tumors are generally benign.

Peritoneal and testicular mesotheliomas have been discussed recently (13, 14) but, despite many reports of individual cases or institutional series of pleural mesothelioma, no recent review of literature on this subject is available. This paper will discuss the natural history of the disease, define its diagnostic features, and evaluate various treatment modalities that have been used. Because Shabanah and Sayegh (10) have recently reviewed the topic of solitary pleural mesothelioma, we will concentrate principally on diffuse pleural mesothelioma and mention the solitary type only as noteworthy differences arise.

Epidemiology

INCIDENCE

Past estimates established by analyzing necropsy series have shown a low incidence of mesothelioma; for example, Hochberg (15) reported a rate of 0.07% based on 43 cases found in 60 042 autopsies. However, recent tumor registries compiled by careful data collection in England, Canada, and the United States indicate that the disease is really not so uncommon (Table 2). Two hundred forty-six cases were identified in England during 1967 and 1968 for an annual incidence of 2.29% cases per million population (4). The current U.S. data from the Third National Cancer Survey (1969-1971) of seven metropolitan areas with a population of 21 million showed 131 cases for a yearly incidence of 2.2 cases per million (16). Similarly, the Connecticut Tumor Registry, which has recorded cancer incidence by site since 1935, showed 24 cases in 1970-1972 for an annual rate of 2.6 per million (personal communication from J.T. Flannery, Connecticut State Department of Health). The apparently equal mesothelioma rates in the U.S. and England are twice as high as the rate of 1.0 per million in Canada (5). The proportion of pleural versus peritoneal tumors is 80% and 20% respectively, in the United States, whereas corresponding

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Table 1. Frequency of Solitary Versus Diffuse Mesotheliomas

Reference	Total Patients	Tumor Type	
		Localized	Diffuse
	no.	no. (%)	no. (%)
(6)	37	6	31
(7)	28	7	21
(8)	18	7	11
(9)	16	8	8
(10)	15	2	13
(11)	13	3	10
(12)	12	1	11
Total	139	34 (25)	105 (75)

rates in England are 88% and 12%. This preponderance of pleural mesothelioma is unexpectedly higher than the 2:1 ratio of pleural versus peritoneal disease reported in the older literature (13, 17). The incidence figures for mesothelioma quoted here are most likely to be underestimated. The true incidence is expected to be higher because until recently mesothelioma was not well accepted and not categorized as such.

ETIOLOGY

With the possible exception of lung cancer, the role of carcinogenic environmental factors in neoplastic disease is most clearly recognized in diffuse pleural mesothelioma. An association between exposure to asbestos and subsequent development of malignant mesotheliomas of the pleura was first suggested by Wagner, Sleggs, and Marchand (18) when they observed an unusually high number of cases within a short time (1956-1960) among the South African asbestos miners. Since this early report many additional studies have clearly implicated asbestos in pleural and peritoneal mesotheliomas found in miners and other workers occupationally exposed in various trades and industries (4, 5, 19-22). Interestingly, evidence generally is lacking for any relation between asbestos exposure and the development of solitary or localized mesotheliomas (10).

Mesotheliomas have been found in all parts of the world but most of the reports have come from areas in England, South Africa, and the United States where asbestos is mined or processed for its many industrial uses. Asbestos is a fibrous silicate of various chemical types such as chrysotile, crocidolite, amosite, and anthophyllite (23). Chrysotile accounts for about 90% of commercial asbestos followed by crocidolite, amosite, and anthophyllite in decreasing order. All types of asbestos have proved to be carcinogenic in humans although there is evidence to suggest that crocidolite may be the most potent (24, 25). Further evidence of the etiologic role of asbestos has been shown in experimental animals where intrapleural injection with asbestos fiber causes mesotheliomas, histologically identical to the human tumor (26, 27). Under these conditions all varieties of asbestos have been carcinogenic in from 8% to 66% of the animals, depending on the dose.

The reported frequency of asbestos exposure in mesothelioma cases varied from 11% to 91% in 16 separate studies reviewed and summarized by Rubino and associates (28). However, a careful analysis of 168 mesothelioma cases in England and South Africa by Elmes (23) placed the incidence of asbestos exposure at 70% (117 cases). Only one third (60 patients) of the total cases could be associated with direct occupational exposure intensive enough to cause asbestosis or lung carcinoma. Another one third (57 cases) were asbestos-related only by trivial contact at work or in the home environment. The remaining 51 cases had no history of contact with asbestos but their exposure could have been forgotten or overlooked (17, 23). Of course, it is possible that unknown etiologic factors may induce the neoplasm. In this connection, Chabot and colleagues (29) have shown the induction of typical mesotheliomas in the chicken by strain MC29 avian leukosis virus.

Perhaps the most convincing evidence of association of asbestos with mesothelioma is brought out by Selikoff, Chrug, and Hammond (19) who reviewed the post mortem findings in more than 300 patients who had been exposed to asbestos. They found a frequency of mesothelioma of 3% in this group, as opposed to a frequency of 0.01 per cent in the general population, thus indicating a 300-fold increase in the frequency of pleural and peritoneal mesothelioma in those exposed to asbestos. In addition, the authors suggested a dose-effect relation by showing a 15% rate of mesothelioma in a separate analysis of patients dying of asbestosis, a fivefold increase over the rate in insulation workers without asbestosis. Similarly Newhouse and Thompson (17) reported an inverse relation between the intensity of asbestos exposure and time to death from mesothelioma, the mean interval between first exposure and death being 29 years in factory workers and 48 years in subjects living near the factory (17). Most other series have reported a similar long interval averaging 30 years between first exposure to asbestos and devel-

Table 2. Incidence of Mesothelioma by Site and Sex

Reference	Population Sample (millions)	Total Mesotheliomas	Sex		Site		Rate (cases/million/yr)
			M	F	Pleural	Peritoneal	
		no.					
United States (16)	21.0	131	92	39	112	19	2.2
Connecticut*	3.1	24	16	8	17	7	2.6
England (4)	53.6	246	201	45	216	30	2.29
Canada (5)	20.0	158	106	52	113	45	1.0

* Flaherty JT: Connecticut State Department of Health, Personal communication.

opment of mesothelioma (3, 4, 18, 30). The duration of asbestos exposure in mesothelioma cases of course has varied from < 1 year to more than 50 years.

Pathology

The variable histologic appearance of pleural mesothelioma simulates other neoplasms so much so that some investigators have challenged the existence of the tumor as a pathologic entity. Indeed, many pathologists only make the diagnosis of "probable mesothelioma," with confirmation resting on factors like failure to find another primary tumor or a history of occupational exposure to asbestos. The pathologic findings have been detailed in a number of recent papers (11, 30-33).

GROSS APPEARANCE

The solitary mesotheliomas are well circumscribed, usually encapsulated, and can arise from parietal or visceral pleura. Most tumors are pedunculated and vary in size from a small mass to one that may occupy the entire hemithorax (10).

Diffuse mesothelioma has a very characteristic macroscopic appearance, which is often of more diagnostic significance than its microscopic features (34). In its earlier stages, the lesions appear as multiple, small white or gray granules, nodules, or flakes on normal or slightly opaque visceral or parietal pleura (6). The tumor tends to spread along the visceral and parietal pleural surfaces, forming a continuous layer encasing the lung and leading to compression atelectasis in advanced cases. With advancing disease, the pleural surface becomes progressively thicker and is generally nodular, or papillary, in appearance. The pleural thickening and other changes are generally more marked near the base of the lung.

The growing tumor extends in all directions, involving the lung, intercostal spaces, and ribs and may even reach the subcutaneous tissues. The diaphragm, liver, pericardium, heart and other mediastinal structures may be involved in advanced cases. In its later stages, the tumor may involve the contralateral pleura and the peritoneum (6, 30, 35). Although diffuse mesothelioma is highly malignant, it is predominantly a locally infiltrative tumor with uncommon distant metastases. The regional lymph nodes are the only common site for metastases except in the advanced stages when the tumor may spread to the other lung and distant organs such as liver, adrenals, brain, and bones (6, 7, 30).

MICROSCOPIC FEATURES

Most of the solitary pleural mesotheliomas are exclusively fibrous, with a mixture of spindle-shaped cells and collagen fibers. Some have areas of epithelial cell elements and in rare instances the entire tumor may be of the epithelial type. These tumors often exhibit considerable cellular atypia in spite of a generally benign clinical course.

The most striking histologic character of diffuse mesothelioma is the remarkable structural variation that may occur between areas in a single tumor or between different tumors having an identical gross appearance. This variability probably stems from the fact that mesothelial cells can differentiate into mesenchymal as well as epithelial elements. The cells of the epithelial type may take various shapes, but most commonly they are cuboidal and are fairly uniform in size and contain vesicular nuclei. Multinucleated forms and occasional mitoses have been observed in some cases but pleomorphism, anaplasia, and atypical mitoses are rare. The cells in mesenchymal types may vary from oval forms through somewhat elongated to distinctly spindle shapes. The mesenchymal cell type may exhibit anaplasia and pleomorphism resembling spindle-cell sarcomas like fibrosarcoma or myosarcoma.

Table 3. Histologic Features of Diffuse Mesothelioma

Reference	Patients	Histologic Type		
		Epithelial	Fibrosarcomatous	Mixed
	no.	no. (%)	no. (%)	no. (%)
(36)	99	45	28	26
(37)	63	34	11	18
(30)	51	22	11	18
(38)	39	29	2	8
(39)	37	25	7	5
(6)	31	16	15	0
(32)	30	21	0	9
(33)	20	11	6	3
(12)	12	5	2	5
Total	382	208 (54.5)	82 (21.5)	92(24)

The proportion of the two mesothelioma cell types is highly variable. The tumor may be purely epithelial or mesenchymal (fibrosarcomatous), or it may contain a mixture of both cell types. The mesothelioma with a particular cell type may have a variety of structural patterns. For example, the epithelial type may be arranged in a tubular or tubulopapillary pattern, or in clefts, solid nests, or sheets. Characteristically, mesotheliomas exhibit more than one pattern and many have a number of patterns. The fibrosarcomatous mesotheliomas consist of sheets of malignant spindle cells or collagenous fibers resembling fibrosarcoma. The bimorphic or mixed mesotheliomas are composed of a mixture of epithelial and fibrous elements.

The frequency of the three main histologic types varies in different series, but our compilation of 382 cases from the literature showed a pattern of 54% epithelial, 25% mixed, and 21% fibrosarcomatous (Table 3). The predominance of the epithelial type was surprising because McCaughey, who first established histologic criteria for diagnosis of malignant mesothelioma (31), reported the presence of the mixed cellular type in more than 50% of 124 autopsied cases. However, he noted that detection of the mixed pattern would have been impossible using only one or two tissue blocks because widely divergent elements usually were not intimately mixed and in most cases occupied adjacent areas or were remote from one another.

in the chest wall, and rib tenderness may be found in cases of advanced disease (30). In cases with advanced disease contraction of the affected hemithorax may occur leading to restriction of chest wall movement and eventually a frozen chest, with flattening of the infraclavicular region, 'roof tiling' of the ribs, and immobility of the chest wall (35).

The tumor has a propensity for growth along the needle tracks after paracentesis or along the scar of a thoracotomy incision (30, 35). Encroachment on the mediastinal structures may lead to neuropathic signs such as vocal cord paralysis or Horner's syndrome (8, 11). The chest wall invasion affecting intercostal nerves often leads to anasthesia or altered sensation in the skin of the chest wall and abdomen. Congestion and edema may develop in the upper trunk or lower limbs because of compression of the superior or inferior vena cava, or both. Ascites caused by peritoneal involvement with the tumor is not uncommon in advanced cases (6, 35, 39).

The systemic effects may produce a variable fever, usually less than 38.3°C. Cachexia and cyanosis are prominent in advanced cases, and death generally is due to pulmonary infection or to cardiac or respiratory failure. Hypertrophic pulmonary osteoarthropathy has been reported (7, 33) but less commonly than in benign pleural mesothelioma. Spontaneous pneumothorax happens occasionally (6) and sometimes may be the first manifestation of the disease (9).

Diagnosis

Diagnosis is generally delayed by an undistinctive clinical picture in early stages of the disease. Malignant mesothelioma should be a consideration in all cases of pleural effusion without obvious cause, particularly when chest pain is a prominent symptom. Unlike the pleuritic pain of inflammatory origin, which usually subsides with effusion, the pain of malignant mesothelioma gradually increases despite the effusion (6). History of exposure to asbestos either by occupation or environment, such as by family contact or by proximate residence, is an important guide to investigate for mesothelioma. Particularly vulnerable occupations are shipyard workers, those working with asbestos textile manufacturing, and brake lining, and insulation workers and sack repair workers.

The differential diagnosis should include inflammatory pleurisy, primary lung cancer, and the presence of metastatic disease from a primary tumor elsewhere in the body. Inflammatory pleurisy can be easily diagnosed by the associated clinical picture and by pleural fluid analyses including cultures of the sputum and pleural fluid. In lung cancer the cough generally is a more prominent symptom, often accompanied by hemoptysis, and chest pain is a late feature of the disease. Additionally, the chest roentgenogram after thoracentesis will show a parenchymal lesion and the pleura will appear quite normal. Sputum cytology generally shows malignant cells in lung cancer but usually is negative in mesothelioma. In spite of these differences, brochiolar carcinoma of the lung can sometimes mimic diffuse mesothelioma so closely that differentiation may be virtually impossible (47). Exclusion of metastatic tumor on clinical grounds alone is most difficult, but a systematic search for a primary tumor must be carried out to exclude this possibility. One must especially exclude an occult carcinoma of pancreas, gastrointestinal tract, and ovary.

Investigations

CHEST ROENTGENOGRAMS

The solitary mesothelioma characteristically appears as a discrete mass, which is of variable size and usually contiguous with one of the pleural surfaces (40). Pleural effusion is unusual, and the lungs and remaining pleura are generally normal.

The characteristic radiographic findings in diffuse mesothelioma have been described by Heller, Janower, and Weber (45) and others (48). Unilateral pleural effusion is the most common abnormality (45, 48). On removal of the fluid, the pleura may show gross thickening or nodularity, which is commonly first noted at the bases. Induced pneumothorax after thoracentesis may aid in showing early thickened pleura or small nodular densities. Late in the disease tomograms or an overpenetrated film will show compressed lung surrounded on all surfaces by a layer of tumor 2 to 3 cm thick. In addition to the mesothelioma induced changes, signs of asbestosis such as interstital pulmonary fibrosis, pleural plaques, and calcification when present are of positive differential-diagnostic value (especially on the contralateral side). Because mesothelioma is commonly not associated with asbestosis, one may need overpenetrated film of the chest to show the characteristic pleural calcification when gross changes are not present. In the later stages, the mediastinum may be widened by involvement of lymph glands. The pericardium may be infiltrated with the tumor and the resulting effusion may enlarge the cardiac silhouette. Extrapleural extension showing as soft-tissue masses or radiologic evidence of rib destruction may occur and are highly suggestive of malignant mesothelioma (48). Hydropneumothorax has occurred rarely.

THORACENTESIS AND PLEURAL FLUID CHARACTERISTICS

One clue to the presence of pleural mesothelioma may be the considerable force needed to enter the pleural space with a thoracentesis needle (34). The pleural fluid is usually straw colored but has been reported to be serosanguineous or frankly hemorrhagic in about 30% to 50% of the cases (6, 7, 15, 49). The effusions generally have a tendency for rapid reaccumulation requiring frequent aspirations, and the fluid becomes increasingly hemorrhagic with repeated taps.

The exfoliative cytology of malignant mesothelioma has been described in detail (50-52). There is considerable difference of opinion concerning its diagnostic value. The pleural fluid generally is very cellular, containing a mixture of normal mesothelial cells, differentiated and undifferentiated malignant mesothelial cells, and varying numbers of lymphocytes, histiocytes, and polymorphonuclear leukocytes (50). In these collected observations 20% of the cases showed no clue to the malignant nature of the

Table 4. Clinical Features of Malignant Mesothelioma

Reference	Patients	Clinical Features						
		Chest Pain	Dyspnea	Pleural Effusion	Cough	Weight Loss	Fever	Others
	no.	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no. (%)	no.
(39)	37	25	17	31	3	4	3	Ascites, 4
(6)	31	28	23	27	10	...	...	Hemoptysis, 2 Pneumothorax, 2
(43)	27	15	22	24	18	13	15	
(7)	21	13	9	13	11	5	7	Hemoptysis, 2
(44)	19	9	13	15	...	10	...	Hemoptysis, 4 Digital clubbing, 2
(33)	19	18	18	15	7	2	...	Digital clubbing, 4
(8)	11	10	7	7	4	4	0	Horner's syndrome, 1
(11)	10	8	10	7	5	...	0	Horner's syndrome, 1 Dysphagia, 1
(45)	10	4	6	4	2	2	...	Hoarseness, 1
(9)	8	4	6	7	2	...	1	Pneumothorax, 1
Total	193	134 (69)	131 (68)	150 (78)	62 (32)	40 (20)	26 (13)	

Clinical Features

AGE

As in most other neoplasms, the greatest number of mesotheliomas occur between the ages of 40 and 60 years. Saccone and Coblenz (34) found that 70% of the patients in a collection of 188 cases were in the 40 to 70 age bracket; Whitewell and Rawcliffe (30) found 74% were between the ages of 50 and 70 in a series of 52 cases. The median age varies between 50 and 60 years in different series, but the tumor does occur at all ages (5, 34). In Hochberg's (15) report on 192 cases, six cases (3.1%) were found in the first decade of life, a similar number in the second decade, and 21 (6.2%) appeared in the third decade. Fifty percent of the cases were diagnosed in patients 50 to 60 years of age.

SEX

In a review of 223 pleural mesotheliomas collected by Hochberg (15), 144 patients were in men and 79 were in women, a sex ratio of 1.8:1. Most series report a ratio of 2:1 but our compilation of 559 recent cases (Table 2) shows a 3:1 ratio.

SYMPTOMS

The solitary mesotheliomas are generally asymptomatic unless the tumor is large and produces localized chest pain and pressure effects (10). Extrathoracic symptoms of pulmonary osteoarthropathy (40) and hypoglycemia are sometimes observed (41, 42).

In diffuse mesothelioma, symptoms may be entirely absent or minimal at the onset of the disease. Disease progression elicits the common symptoms of chest pain, dyspnea, cough, and gradually increasing weight loss accompanied by pronounced asthenia (6, 7, 15, 34). Chest pain is the most common complaint and eventually becomes the incapacitating symptom in most patients (Table 4). Because it is caused by infiltration of the chest wall the pain is usually localized over the involved side but may radiate to the shoulder and arm. It commonly has a dull gnawing quality but may vary from mild discomfort to a severe neuralgic pain and rarely has a pleuritic quality. Dyspnea is proportional to the disease stage, occurring with physical exertion in the beginning but later becoming a constant symptom. The cough is a less common symptom and is not usually present until the disease encroaches on the mediastinum. Then, it may become quite persistent, dry, and irritational although at times there may be slight hemoptysis (6, 11). Some patients have irregular episodes of low-grade fever.

The later stages of disease are marked by aggravation of all symptoms, poor appetite, and rapid weight loss. In the terminal stages there is marked dyspnea, orthopnea, diaphoresis, cachexia, and severe chest pain that is only partially relieved by large doses of narcotics. Rarer symptoms include arthralgic pain with hypertrophic pulmonary osteoarthropathy (6, 33), syncopal attacks from hypoglycemia (46), and generalized anasarca from pericardial involvement or obstruction of the inferior and superior vena cavae (6). Dysphagia (6), hoarseness, and back pain have occasionally been reported.

PHYSICAL FINDINGS

The solitary mesotheliomas present few physical signs. Patients usually show signs of a localized chest mass, and, in rare instances, there may be a pleural effusion that is sometimes hemorrhagic (7).

In diffuse mesothelioma the physical findings vary with the disease stage. Most patients initially present with signs of fluid in the involved hemithorax (Table 4). In the more advanced disease local chest involvement is more marked and there may be obvious enlargement of the affected hemithorax, bulging of intercostal spaces, and displacement of the trachea and mediastinum to the unaffected side (6). Local tumor growth may also depress the diaphragm and displace the liver and spleen, giving the impression of hepatomegaly or splenomegaly. A pericardial or pleuropericardial rub is not uncommonly heard after removal of all the pleural fluid. Supraclavicular and axillary lymph node enlargement, subcutaneous nodules

rent tumors, after resection of solitary benign mesothelioma, are usually malignant but benign recurrences are occasionally reported (10). Because solitary mesotheliomas are not always benign, radical excision, perhaps combined with radiotherapy and chemotherapy, should be used in malignant tumors. Malignancy in solitary tumors is not uncommon in childhood mesotheliomas (67), and of course the fibrosarcomatous variety of diffuse mesothelioma may initially present as a localized tumor (6).

The therapy of diffuse pleural mesothelioma presents problems that have never been clearly defined. The various treatment modalities have included surgery, external radiotherapy, intracavitary radioisotopes, cytotoxic drugs, and various combination of these approaches.

SURGERY

Because of the extensive infiltration of adjoining viscera, the diffuse pleural mesotheliomas pose a difficult problem for complete extirpation. However, in spite of the technical difficulties, data are available on approximately 400 patients who have undergone surgery of variable extent (68). "Curative" surgery, consisting of pleuropneumonectomy, was attempted in 62 cases by Worn (69), in 17 cases by Bamler and Maaben (70), and in five cases by Schamaun (71). More often these investigators used palliative surgery, generally confined to parietal pleurectomy and removal of the bulk of remaining tumor. It is difficult to judge whether survival was prolonged in these uncontrolled series but it is clear that a substantial mortality rate (20% in the series of Bamler and Maaben) accompanied the radical procedure. Because the survival rate was no better than that obtained with palliative surgery, parietal pleurectomy alone is the preferred form of treatment.

A more recent study of Martini, Bains, and Beattie (72) further supports the feasibility of parietal pleurectomy for controlling pleural effusion without significant operative mortality. Worn's 1-year survival rate of 70% (140/200) and the 79% (11/14) reported by Martini and colleagues (72) are vastly superior to the generally accepted 30% 1-year survival rate after diagnosis of diffuse mesothelioma (15, 34, 35). Postoperative adjuvant chemotherapy and radiotherapy of unspecified extent were used in both studies and may have been influential in the increased survival rate. By comparison, Schuster and Huzly (73) used parietal pleurectomy without supplemental treatment in 98 patients and reported only a 24% 1-year survival rate.

EXTERNAL RADIOTHERAPY

The value of radiotherapy is commonly recognized for controlling pain and pleural effusion in mesothelioma. However, three recent U.S. studies (3, 6, 39) imply that, in spite of the palliative benefits, this modality is relatively ineffective against the disease. There are also reports indicating that chest irradiation in mesothelioma is totally ineffective and may even be detrimental (49).

On the other hand, some investigators have reported objective control of the disease by radiotherapy (12, 38, 74, 75). The most impressive data were reported by Schlienger and his associates (38, 75) who treated 46 patients. There was relatively little benefit with total doses of <3500 rad (38), but at a median dose of 4500 rad (range, 3500 to 7500 rad), the median postirradiation survival was 15 months (range, 1 to 37 months). Anatomical regression of tumor was noted in several cases and patients tolerated the therapy without significant complications. This group advocated use of irradiation at higher than the commonly used doses and felt that the therapy was definitely beneficial.

Table 8. Survival in Malignant Pleural Mesothelioma

Reference	Patients	Average Survival from Onset of Symptoms	Remarks
	no.	months	
(3)	72*	15	Treated with radiotherapy or chemotherapy, or both
(30)	36	12	One third of patients survived beyond 2 years
(39)	34	12	75% died within 12 months
(6)	31	20	Intensive combination of surgery, chemotherapy, and radiotherapy; post-therapy survival averaged 14 months
(39)	28	12	Radiotherapy routinely used
(43)	27	10	Most cases treated surgically
(33)	20	...	17/20 died within 12 months of onset
(44)	19	10	Only four patients lived beyond 1 year
Total	267	12.5†	

* Includes some cases of peritoneal mesothelioma.
† Median = 12 months.

Radioactive Colloidal Gold (^{198}Au)

Colloidal ^{198}Au has been used successfully by some investigators for controlling pleural effusion (76-79). Smart and Hinson (76) reported the resolution of pleural effusion in seven of 10 cases and Strashinin and Chupin (77) achieved similar results in four of six cases treated with intrapleural ^{198}Au. Long-term control has been achieved in some instances (77, 78). The generally recommended dose of 50 to 100 mCi, repeated in 3 to 6 months, has not caused significant toxicity. The treatment is most beneficial in early cases before the pleural cavity is obliterated by the tumor.

CHEMOTHERAPY

The role of cytotoxic drugs in mesothelioma has not been systematically explored but there are well-documented reports of definite antitumor effects in some patients. Alkylating agents such as cyclophosphamide (80), nitrogen mustard (81), and thio-TEPA (46) possess some activity and occasionally have induced complete regressions. Approximately 30% of the patients treated with alkylating agents have experienced some degree of objective response (68).

Other reportedly active antitumor drugs include doxorubicin (adriamycin) (82) and 5-fluorouracil (83). Doxo-

pleural fluid (50-52). Undifferentiated malignant cells without mesothelial cell characteristics were found in another 20% of the cases. Approximately 50% to 60% of the cases had typical mesothelial cells, which could be identified by observers familiar with the wide range of appearances shown by mesothelial cells. Typical mesothelial cells are rounded, somewhat larger than a histiocyte, with an abundant dense eosiniphilic cytoplasm and a small rounded nucleus containing a prominent nucleolus. Many of the cells are multinucleated. The cells tend to form clusters with knobby outline.

The diagnostic value of cytology is limited because of the subtle differences between benign and malignant mesothelial cells. Mesothelial hyperplasia and hypertrophy is not uncommon in benign pleural effusions, and the cells can be easily mistaken for malignant cells and vice versa. With these limitations, cytology should only be a guide to a provisional diagnosis of mesothelioma that should be subsequently confirmed by biopsy in all cases.

CHEMICAL FINDINGS

The fluid usually is an exudate with high protein concentration ranging from 3.5 to 5.5 g/dl (8, 11). Taryle, Lakshminarayan, and Sahn (8) have reported elevated lactic dehydrogenase level (> 600 IU in some cases) and decreased glucose in a proportion of cases (8).

Detection of an elevated concentration of acid mucopolysaccharide (AMP), mainly hyaluronic acid, in the serous effusion fluid has been considered helpful in the diagnosis of diffuse mesothelioma. Harington, Wagner, and Smith (53) first reported hyaluronic acid levels of 120 to 7900 μg/ml of fluid in six biopsy-proven cases of mesothelioma. Similarly, Thompson, Bromberg, and Amenta (54) noted elevated concentration in three patients with malignant mesothelioma and undetectable levels in eight patients with pleural effusions of other origin. Castor and Naylor (55) in a series of 100 cases of pleural effusion of diverse causes showed that the concentrations of AMP were increased in many benign and malignant effusions but were generally below 120 μg/ml in benign conditions and above this level in malignancies including mesothelioma. Similar results were obtained by Rasmussen and Farber (56) in 247 cases of pleural effusion. Hyaluronic acid was present in many cases of transudative effusions but the level was generally less than 0.2 mg/ml. Values of 0.2 mg to 0.8 mg/ml occurred in fluids from different types of inflammation and malignancy (including some cases of mesothelioma) but those greater than 0.8 mg were found only in mesotheliomas. However only seven of 19 mesothelioma cases had hyaluronic acid level higher than 0.8 mg/ml; the rest had levels between 0 to 0.8 mg distributed fairly uniformly. Therefore elevated AMP is far from being a specific and is only moderately sensitive test for the differential diagnosis of mesothelioma. When the concentration of AMP is very high, the fluid is characteristically viscous and the appearance should lead one to consider the possibility of an underlying mesothelioma (56).

Some investigators have used histochemical methods of detecting AMP in the pleural biopsy tissue of mesotheliomas (32, 57, 58). Alcian blue and Hale's colloidal iron stains produce a characteristic metachromatic reaction to AMP in the mesothelioma. These reactions are considerably reduced or abolished by previous digestion with hyaluronidase (32). Because AMP may occur in any rapidly growing connective tissue, its presence has diagnostic significance only when associated with epithelial mesothelioma.

In contrast to adenocarcinomas, mesotheliomas do not stain with the periodic acid Schiff (PAS) reagent or with mucicarmine (59). The intracellular or intratubular mucin of adenocarcinomas usually will take the PAS or mucicarmine, but not invariably. Although they are often useful, histochemical tests lack consistency and should be interpreted with caution (7, 60).

THORACOTOMY

An open thoracotomy is generally required to furnish sufficient material for a correct diagnosis by the pathologist. Multiple biopsies from different pleural areas should be taken because of the variable histology seen in various parts of the tumor. The gross pathology at thoracotomy is usually characteristic and suggests the diagnosis to the experienced clinician. Final diagnosis rests on detailed histologic examination aided by histochemical studies.

Electron microscopy recently has been used in mesothelioma and may have additional diagnostic value in difficult cases (61-62). These studies can be especially helpful in differentiating diffuse mesothelioma from bronchioloalveolar carcinoma, which sometimes resembles it (61, 63).

Demonstration of asbestos bodies in the sputum or biopsy material has been an additional diagnostic aid in suspected mesothelioma (37, 64). They can be best shown in touch preparations made from the fluid squeezed from the fresh tissue (65). Although this finding is useful, it simply implies probable exposure, in that asbestos bodies have been observed in the sputa of many healthy individuals throughout the United States (64).

OTHER STUDIES

Scalene node biopsy has been used when the lymph nodes are palpable, which may occur in advanced cases (6).

Thoracoscopy is difficult because of the frequent symphysis of pleural surfaces, but it is possible to visualize the pleural surface in early disease. When the pleura is thin and effusion is clear, discrete pleural nodules can be seen overlying the still elastic lung. The nodules are usually cherry colored and either smoothly rounded or warty in appearance. Later, the discrete nodules coalesce and the underlying lung is obscured. The growth then appears as a gray opaque membrane with localized excrescences of variable size. The lung becomes completely immobile and incarcerated at the later stages of disease (35).

Treatment

Surgical excision is generally curative in most patients with solitary mesothelioma but local recurrence takes place in a small percentage of these cases (10, 66). Recur-

rubicin therapy induced two complete and three partial responses in five patients treated by Kucuksu, Thomas, and Ezdinli (82). Similarly, Gerner and Moore (83) treated three patients with 5-fluorouracil and reported two complete regressions lasting 18 months in each case.

Combination chemotherapy has not been extensively studied but regimens containing doxorubicin appear to have quite consistent effectiveness. Gottlieb and associates (84) have reported that doxorubicin plus 5-(3,3-dimethyl-1-triazeno) imidazole-4-carboxamide (DTIC or DIC) was useful in some cases of mesothelioma. Gottlieb and associates (85) also reported that a combination of cyclophosphamide, vincristine, doxorubicin, and DTIC, known as CY-VA-DIC, exhibited good activity. Another four-drug combination termed "COMF," consisting of cyclophosphamide, vincristine, methotrexate, and 5-fluorouracil also is reported active against mesothelioma (82).

These reports are encouraging and indicate the need for properly evaluating the role of chemotherapy in prospective trials. Whether combinations of drugs are superior to single agents remains to be proved.

COMBINED MODALITIES

The available data for therapeutic results do not indicate the superiority of any individual treatment modality, and complete eradication of tumor is infrequent with any of them. The studies that have produced above-average survival rates have used combinations of therapies such as surgery followed by external radiotherapy and, when possible, by systemic chemotherapy (6, 69, 72). In the only study reporting 5-year survival (9%), the therapeutic approach consisted of surgical resection plus radiotherapy and chemotherapy (69). Martini and colleagues (72) recently were encouraged by their use of surgery, external irradiation, and chemotherapy in obtaining a post-treatment median survival duration of 16 months in a small group of patients.

Although none of the studies were controlled, they strongly support the need for evaluating combined-modality approaches in well-designed prospective trials. In general, the lack of success in altering the fatal course of diffuse mesothelioma through single modalities of treatment, and the recent progress using combined modalities against resistant tumors like osteosarcoma (86, 87), favor exploration of multimodality treatment approaches in malignant mesothelioma.

Conclusion

Diffuse pleural mesothelioma is a highly malignant disease with an average survival from onset of symptoms of 12 to 15 months (Table 5). There is usually a delay of 6 to 8 months before the diagnosis is established (6, 7, 39), and most of the patients (approximately 75%) are dead within 1 year after diagnosis. The average survival after diagnosis is 8 to 10 months. The delay in diagnosis is responsible for the advanced disease stage at the time therapeutic intervention is sought. In the past, treatment has been generally unsuccessful in altering the course of the disease. More recently, there appears to be some optimism with the use of chemotherapy as well as more aggressive forms of chest irradiation.

In general optimal response to various therapeutic modalities is most likely when the tumor is diagnosed and treated early. Most cases of mesothelioma unfortunately are far advanced at the time of diagnosis, and the patient is physically in a poor condition. Mesothelioma should be considered a possibility in all cases of pleural effusion without obvious cause. A history of exposure to asbestos should make one suspect the presence of this tumor, especially when pleural effusion is accompanied by severe chest pain. In the future, increasing recognition of this entity and a more aggressive approach to early diagnosis and to therapy may improve the survival in this not uncommon type of cancer.

ACKNOWLEDGMENTS: The authors thank Ms. Kuldip K. Legha and Mr. William Soper for their valuable assistance in the preparation of this paper.

Received 8 December 1976; revision accepted 14 January 1977.

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