

Malignant Mesothelioma: A Disease that Continues to Mystify

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There are few diseases that demonstrate such a direct relation between cause and effect as malignant mesothelioma with asbestos exposure. In the past decade the rate dramatically increased and will probably continue to rise in the next 10 years, reflecting the widespread use of asbestos during industrialization in developing countries. Owing to the long incubation period (as long as 30 years) between the onset of disease and the time of first exposure, this epidemic did not occur immediately [1].

Malignant mesothelioma is an aggressive tumor that arises from the mesothelial surfaces of the pleura and the peritoneum cavities, and less commonly from the pericardium and the tunica vaginalis [2-4]. Asbestos is the principal carcinogen associated with malignant mesothelioma but other etiologic factors – such as the Simian virus 40 [5,6] or therapeutic irradiation – have been implicated in development of the disease [7].

There are two types of asbestos fibers – the thin and long amphiboles (blue asbestos) and the feather chrysotiles (white asbestos). It is the thin amphiboles that cause mesothelioma. After inhalation, the thin fibers penetrate the lung, irritate the pleural space leading to scarring (plaques), interfere with the mitotic process, and generate toxic oxygen radicals leading to chromosomal damage. They also increase the expression of proto-oncogenes that encode members of the Fos Jun and activator protein 1 families [8].

Molecular studies suggest that a genetic susceptibility to asbestos-induced tumor formation may also be at play. Loss of chromosome 22 is the most common gross change, but structural rearrangement of 1p, 3p, 9p and 6q has been noted. Simian virus 40 (SV 40) is a DNA virus that blocks tumor suppressor genes and is a potent oncogene in human and rodent cells. SV 40 DNA sequences are found in brain and bone tumors, lymphoma as well as in atypical mesotheliomal proliferations. There is some evidence that SV 40 may have been inadvertently transmitted to humans in injected poliomyelitis vaccines 35–50 years ago.

Other rare cases of malignant mesothelioma have been associated with therapeutic irradiation and intrapleural thorium dioxide [7]. Peritoneal mesothelioma is quite rare compared to pleural mesothelioma (30% of all mesotheliomas). Local invasion is the common cause of morbidity and mortality: Patients with pleural mesothelioma present with pleural effusion associated with breathlessness and chest pain. Patients with peritoneal mesothelioma present with abdominal distension and pain due to ascites and occasionally bowel obstruction. The disease is

generally localized to the peritoneal cavity and does not infiltrate the liver parenchyma. In the advanced stage, direct extension to the pleural cavity and distal metastases occur. The prognosis of the disease is poor, with survival ranging from 7 to 13 months [2,3].

There are three principal types of mesothelioma: the epithelial type (tubulopapillary, non-glandular/solid), the sarcomatoid type, and the mixed type. A favorable prognosis has been reported with the tubulopapillary variant of the epithelial type. Fifty percent of pleural mesotheliomas and 75% of peritoneal mesotheliomas are of the epithelial type.

Rapid diagnosis is essential for making therapeutic decisions. Immunohistochemical staining is helpful to determine the origin (to distinguish it from adenocarcinoma) and the invasion of the tumor. Calretinin, cytokeratin antibodies CK5/6, and Wilm's tumor antigen are positive in mesothelioma, but carcinoembryonic antigen and Leu-M1 are usually negative in mesothelioma tumor [9].

Serum markers may help in the follow-up of the patients. Serum mesothelin-related protein, the circulating product of mesothelin, is elevated in 84% of patients with mesothelioma and fewer than 2% of patients with other lung diseases. The SMRP level parallels the progression and resection of the tumor and may be used in monitoring therapy and for early detection in patients who had been exposed to asbestos [10]. Osteopontin is another promising marker. It is a glycoprotein that is over-expressed in patients with mesothelioma but is also elevated in other cancers (gastric, colorectal, pancreatic, lung, ovarian) [11].

Patients with peritoneal mesothelioma may have a more favorable prognosis as compared to pleural mesothelioma. Peritoneal mesothelioma is treated by palliative surgery for the relief of small bowel obstruction or massive ascites, and by radiation therapy or chemotherapy. Trials of multimodality surgery combining both cytoreductive surgery and intraperitoneal chemotherapy have resulted in improved survival, especially in solitary well-differentiated papillary mesothelioma. Goldblum and Hart [12] found that tumors with tubuloepithelial pattern and low grade nuclei behave in a benign manner. Kerrigan et al. [13] noted that a substantial proportion of diffuse peritoneal epithelial mesothelioma behaves indolently (40% survival after 4 years). Other studies report a median survival of 58 months [14]. All peritoneal

SMRP = serum mesothelin-related protein

mesotheliomas should be treated with a view to cure and long-term survival. Immunotherapy, gene therapy (suicide gene therapy and immunomodulatory therapy) are still in the early stage of development. Alimta® (Eli Lilly, USA), a novel antifolate drug, shows increased survival in pleural mesothelioma.

In this issue of the journal two case reports relate to the subject. Hershcovici and co-authors [15] describe two patients with malignant peritoneal mesothelioma associated with familial Mediterranean fever. The patients had not been exposed to asbestos, and the diagnosis was supported by immunohistochemical stain (calretinin). These two cases are interesting and suggest recurrent serosal inflammation as a cause of mesothelioma development. In the context of such rare entities, association is quite reasonable. In the other article, Machlenkin and associates [16] report the case of benign cystic mesothelioma of the peritoneum. This rare neoplasm of the peritoneum consists of solitary or multiples cysts arising from the mesothelial cells. Although its etiology remains unclear, infections, foreign bodies, endometriosis or peritoneal irritation have been hypothesized as risk factors. Surgical resection is helpful but the rate of recurrence is high [17,18].

We still have much to learn about the pathogenesis of malignant and benign mesothelioma. Aggressive therapy is needed in every case since we do not yet have identifiable factors to predict a favorable versus unfavorable course. In the meantime, new drugs like Alimta may increase survival and hold out some hope against this fatal disease.

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