Two Familial Mesothelioma Cases with High Concentrations of Soluble Cytokeratin 19 Fragment in Pleural Fluid

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We report two cases of diffuse malignant pleural mesothelioma occurring almost simultaneously in one family. Patient 1 was a 42-year-old Japanese man who had worked as an electrical engineer for 25 years. Patient 2, his mother, was 69 years old. She lived for 10 years with patient 1 after he started his work, and also worked at a shipyard herself for 6 years. The concentrations of cytokeratin subunit 19 fragment (CYFRA 21-1) in pleural fluid of the two patients were 1,500 ng/ml and 1,200 ng/ml, respectively. Measurement of CYFRA 21-1 concentration in the pleural fluid may be a useful tool for a diagnosis of malignant mesothelioma.

Key words: occupational asbestos exposure, open biopsy via thoracotomy, quantitative asbestos digestion study, tumor marker

Introduction

Malignant mesothelioma is a rare but aggressive tumor which is frequently associated with asbestos exposure. Kure City has been known to be one of the major ship building cities in Japan since before World War II, and it is reported that the incidence of mesothelioma in Kure City has been recently increased (1). Familial clustering of malignant mesothelioma has been reported in patients from Western populations (2, 3), but never in Japan. This is the first report of familial mesothelioma in Japan.

Case Report

Patient 1

Patient 1, a 42-year-old Japanese man had worked as an electrical engineer for approximately 25 years till the present age. He had an occupational exposure to asbestos in handling insulators and in wiring for electricity. He had also been a cigarette smoker for 20 years and his Brinkman index was counted as 500. His father died of lung cancer two years before the patient started his work, but his sister and his own two sons had been in good health. In June 1995, the patient was admitted to Kure Kyosai hospital because of dyspnea on exertion. A chest radiograph showed a right pleural effusion and ipsilateral apical pleural thickening. Moreover, a computed tomographic (CT) scan of the chest revealed a right paratracheal lymphadenopathy (Fig. 1). A thoracocentesis revealed the pleural effusion to be an exudate with a lymphocytic predominance. The hyaluronic acid concentration was 1,260 mcg/ml, the carcinoembryonic antigen (CEA) concentration was 1.3 ng/ml, and the concentration of cytokeratin subunit 19 fragment (CYFRA 21-1) was 1,500 ng/ml. The effusion showed many mesothelial cells, which were immunohistochemically positive for epithelial membrane antigen (EMA) and CA 125 but negative for CEA. Even with these results it was difficult to diagnose conclusively that these cells were malignant mesothelioma cells because they lacked definite atypism as malignant cells cytologically. At open biopsy via thoracotomy, many nodules were found to be diffusely distributed on both the visceral and parietal pleura of the right pleural cavity; the largest nodule at the apex portion showed direct invasion of the chest wall. Histologic examination of the specimens taken from the nodules of the parietal pleura showed the picture of biphasic mesothelioma (Fig. 2A). By an immunohistochemical study (4), almost all the tumor cells were found to show positive reactivity for monoclonal anti-cytokeratin 19 fragment antibody (from Boehringer-Mannheim for immunohistochemical...
Figure 1. Chest CT after thoracentesis shows right apical pleural thickening and ipsilateral paratracheal lymphadenopathy (patient 1).

use) (Fig. 2B). A quantitative asbestos digestion study (5) of biopsied lung tissue showed 86 asbestos bodies per 5 g of wet lung tissue. After a staging procedure, the patient was found to be in stage 3 according to the system of Butchart et al (6), and also in stage 4 (T3N3M0) according to the UICC TNM staging system.

Patient 2
Patient 2, the mother of patient 1, was a 69-year-old Japanese woman. She had a distant history of work at a ship yard for 4 years and at a steel plant for 2 years. She had lived with Patient 1 for approximately 10 years after he began working as an electrical engineer. She had never been a cigarette smoker. She was admitted to Kure Kyosai hospital because of a subcutaneous nodule found on the abdominal wall in June 1995, two weeks after the day when patient 1 was admitted. A chest radiograph showed a right pleural effusion. A needle biopsy specimen of the subcutaneous nodule contained some mesothelial cells; however, a definite diagnosis of malignancy was not made because they lacked the nuclear atypism histologically. A chest CT scan did not show pleural thickening or mediastinal lymphadenopathy, and it showed only slight left pleural effusion (Fig. 3). A thoracocentesis revealed an exudate with a predominance of histiocytes. The pleural fluid concentration of hyaluronic acid was 290 mcg/ml, that of CEA was 0.7 ng/ml, and that of CYFRA 21–1 was 1,200 ng/ml. Cytologic examination showed many mesothelial cells suggestive of malignant mesothelioma, with positive immunostaining for EMA and CA 125 but not CEA. An open biopsy showed flat small nodules diffusely distributed on both the visceral and parietal pleural surfaces. These nodules were confirmed to show the picture of biphasic mesothelioma histologically (Fig. 4A). Immunohistochemical findings of tumor cells using monoclonal anticytokeratin 19 fragment antibody was similar to those found in patient 1 (Fig. 4B). Quantitative asbestos analysis of biopsied lung tissue showed only eight asbestos bodies per 5 g of wet lung tissue. The patient’s clinical stage was stage 4 according to both Butchart’s and UICC’s systems.

Discussion

Malignant pleural mesothelioma is a rare tumor. Chemotherapy or radiation therapy have a poor effect on the progression of this tumor, so that overall, the mean survival in patients with malignant pleural mesothelioma is less than 1 year after the diagnosis is made. Mesothelioma is closely associated with asbestos exposure. The incidence of mesothelioma in people with prolonged heavy exposure to asbestos is 2% to 10%, and the latency period between initial exposure and manifestation of disease is usually 20 to 50 years. It is not clear why one person with occupational exposure to asbestos develops a mesotheli-
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Figure 3. Chest CT after thoracentesis shows only slight pleural effusion on the left without pleural thickening or mediastinal lymphadenopathy (patient 2).

Figure 4. Histological findings of biopsy specimen in patient 2. A) Tumor cells with cuboidal or spindle-shaped cytoplasm infiltrate the pleura as well as in the connective tissue (HE stain, ×100). B) Marked reactivity is present in the cytoplasm of almost all the tumor cells for monoclonal anti-cytokeratin 19 fragment antibody. The epithelial component is stained to the same degree as the sarcomatous area (alkaline phosphatase-labeled avidin and new fuchsin, counterstain HE, ×100).

lion and another person with exactly the same exposure does not, nor why approximately 20% of patients with mesothelioma lack a history of asbestos exposure (7). In recent years, the incidence of mesothelioma has increased as a result of the widespread occupational use of asbestos.

Kure City has had an active ship building industry since it became a naval port in the 1920s. Therefore, the number of malignant mesothelioma patients in Kure City has recently risen (1). Though familial clustering of malignant mesothelioma has previously been reported in Western countries (2, 3), it has not been reported in Japan. This is therefore the first report of familial mesothelioma in our country to our knowledge.

Household contamination with asbestos from clothing occurred commonly in familial mesothelioma cases of Western countries. Patient 1, the son, had an occupational exposure to asbestos for about 20 years. However 5 g of biopsied lung tissue from patient 1 contained only 86 asbestos bodies, with 37 ferrous bodies and 49 naked bodies. Patient 2, the mother of patient 1, had an occupational exposure to asbestos for 6 years and also had indirect asbestos exposure at home from patient 1. She had only eight asbestos bodies per 5 g of biopsied lung tissue, all of which were naked bodies. Asbestos exposure cannot be excluded as a cause of the familial cases reported here, because cases of mesothelioma may be associated with minimal exposure to asbestos. However, the Wilms' tumor susceptibility gene (WT1) (8), the neurofibromatosis type 2 (NF2) gene (9), and simian virus 40-like DNA sequence (10), are detected at high levels in mesothelioma. In the familial cases reported here, a genetic factor may have been responsible for the mesotheliomas, because of the low asbestos load in the lung tissue.

It has been suggested that a high pleural fluid concentration of hyaluronic acid is a strong indication of malignant mesothelioma, but it is not specific for malignant mesothelioma and can occur in other malignant or benign diseases. Cytokeratin fragments have been subdivided into 19 different types according to their molecular weight and isoelectric point, as determined by two-dimensional electrophoresis (11). A new tumor marker, CYFRA 21-1, is defined by a sandwich enzyme-linked immunosorbent assay which detects and measures soluble cytokeratin 19 fragments in serum, using two specific monoclonal antibodies, KS 19-1 and BM 19-21 (12). Serum CYFRA 21-1 is highly associated with lung cancer, especially squamous cell lung cancer (13, 14). Whereas the diagnostic value of CYFRA 21-1 in pleural fluid is unclear. We obtained 32 benign pleural effusion cases (liver cirrhosis: 2 cases; pleuritis; 3 cases; pleuropneumonia; 4 cases; tuberculosis pleurisy; 11 cases; empyema; 2 cases; heart failure; 7 cases; benign asbestos pleural effusion; 3 cases). In our study, the concentrations of CYFRA 21-1 in pleural fluids of these two mesothelioma cases were significantly higher than those of benign
diseases (median: 23.5 ng/ml; interquartile range (IR): 8.1–36.0 ng/ml; Mann-Whitney U test: p<0.02). Normal mesothelial cells and mesothelioma cells synthesize keratins and vimentins (15). It is not clear why mesothelioma cases showed high concentrations of CYFRA 21-1 in pleural fluid though benign mesothelial proliferation diseases showed low concentrations. Mesothelioma cells may synthesize much more cytokeratin than normal mesothelial cells. And or high CYFRA 21-1 concentrations in the pleural fluid may originate from the number of mesothelioma cells, i.e., tumor bulk. In the cases reported here, the pleural fluid concentrations of CEA were low, but those of CYFRA 21-1 were extremely high. CEA is usually high in malignant epithelial tumors. These results suggest that measurement of CYFRA 21-1 in pleural fluid may be useful in the diagnosis of malignant pleural mesothelioma. Further studies of CYFRA 21-1 in mesothelioma are needed.

References