Malignant pericardial mesothelioma following thoracal radiotherapy; dissemination from pericardium to pleura

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ÖZET

Torakal radyoterapi sonrası gelişen malign perikardiyal mezotelyoma; perikarttan plevraya yayılım


Anahtar Kelimeler: Asbestozis, malign mezotelyoma, perikart, plevra, radyoterapi.

SUMMARY

Malignant pericardial mesothelioma following thoracal radiotherapy; dissemination from pericardium to pleura

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Malignant pericardial mesothelioma (MPeM) is a rare, primary pericardial tumor of mesodermal-origin. With respect to the etiology of MPeM, a history of exposure to asbestos has not been clearly demonstrated. MPeM is difficult to diagnose because of the non-specificity of the clinical complaints and symptoms. A known effective treatment does not exist and the prognosis is poor. In this case study, the possible etiologies of MPeM are discussed based on the extant literature. We report herein a patient with MPeM and no history of asbestos exposure who had chemo-radiotherapy for non-Hodgkin’s lymphoma, and in whom a tumor spread from the pericardium through the pleura.

Key Words: Asbestosis, malignant mesothelioma, pericardium, pleura, radiotherapy.

Malignant mesothelioma is an aggressive and malignant tumor that is occurring throughout the world with an increasing prevalence; unfortunately, there are limited treatment options for malignant mesothelioma (1). Frequently, malignant mesothelioma develops through the mesothelial surfaces of the pleural and peritoneal cavities, and rarely, through the pericardium and tunica vaginalis (2). Although a relationship between asbestos exposure and the development of mesothelioma has been clearly observed, not all patients with malignant mesothelioma have a history of asbestos exposure. Other possible causes of malignant mesothelioma include the simian 40 virus, non-asbestos mineral fibers, organic chemical substances, and radiotherapy (3).

Primary tumors of the pericardium are rarely observed. Malignant pericardial mesothelioma (MPeM) is the most frequent primary pericardial tumor and comprises approximately 50% of all primary pericardial tumors (4). In a Canadian epidemiologic study, the annual incidence of MPeM was reported to be 1 in 40 million (5). In another study which focused on 1785 cases of malignant mesothelioma detected between the years 1958 and 1996, only 6.1% of the cases were reported to be MPeM (6). Approximately 150 cases of MPeM have been described in the literature, of which most have been reported as case studies. Today, the etiology of MPeM is not completely known. The relationship between asbestos exposure and MPeM has not been clearly established (7). It has been reported that there is a possibility for MPeM to develop after radiotherapy applied to the thorax for various reasons (8,9).

Our aim in reporting this case was to contribute information pertaining to the etiology of MPeM by describing a patient with no history of asbestos exposure in whom MPeM was assumed to have developed secondary to radiotherapy administered in the treatment of non-Hodgkin’s lymphoma; detected to have spread through the pleural cavity as a result of treatment. The causal relationship between radiotherapy and MPeM is discussed together with information existing in the literature. We also hoped to emphasize the many obstacles which occur during the diagnosis and treatment of MPeM.

CASE REPORT

A 40 year-old male patient was admitted to our clinic with dyspnea in October 2005. In addition to the dyspnea, there was chest pain. In 1978, non-Hodgkin’s lymphoma was diagnosed and the patient was treated with radiotherapy; chemotherapy with the COPP regimen (cyclophosphamide, vincristine, procarbazine, and prednisolone) was instituted because of a relapse in 1983. The patient had a gastrectomy after a diagnosis of gastric lymphoma in 1998, for which he had chemotherapy with the CHOP (cyclophosphamid, vincristine, doxorubicin, and prednisolone). He was admitted to a chest clinic of another hospital in December 2004 with a complaint of dyspnea, which had existed for three months. With the assistance of the medical oncology-haematology and cardiology departments, pericardial fluid was identified. In this period, a chest computerized tomography (CT) scan demonstrated a moderate pericardial effusions and mild left-sided pleural effusions. There was no reliable evidence to speculate a diagnosis of pleural or pericardial mesothelioma at that time. Assuming that the cause of the pericardial fluid was mediastinal drainage reduction, a pericardial-pleural window was recommended as a method of treatment, and a pericardial-pleural window was opened in July 2005. Non-specific findings were observed during the histopathological analysis of the obtained pericardial specimen, and a specific diagnosis was not established.
The patient gave no history of consuming alcohol or smoking cigarettes, he did not use any medication on a long-term basis, and he had no exposure to asbestos.

On physical examination at the time of admission, the sound of the heart beat was deep, the breath sounds were diminished at the left lung base, and dullness was appreciated in the lower left lobe by percussion. The laboratory analysis was significant for a sedimentation rate of 48 mm/hour and a C-reactive protein of 7.9 mg/dL; the hematological tests were within normal limits. A posteroanterior chest radiograph showed a left pleural effusion and an enlarged cardiac shadow. Echocardiography (ECHO) revealed irregularly thickening pericardium invaded to the epicardium with a small amount of fluid in the back walls of the left and right ventricles.

The pleural effusion was predominantly lymphocytic and had an exudate from the albumin gradient. The pleural fluid ADA value was 8 IU/L (ranges, 0-40 IU/L). A purified protein derivative (PPD) test had a 2 mm induration. The pleural effusion lymphoma panels did not reveal a marked characteristic. The pleural effusion cytologic analysis showed atypical cells, suggesting malignancy. A CT scan of the thorax revealed irregular pericardial thickening and fluid, a pleural effusion on the left side, and fibrotic changes secondary to radiotherapy in the pulmonary parenchyma (Figure 1). A magnetic resonance imaging (MRI) of the thorax showed an irregular, limited mass that entirely surrounded the pericardium, located on the anterior wall of the right ventricle adjacent to the apex, and on the inferior segment of the left ventricle, with invasion to the epicardium (Figure 2). The positron emission tomography (PET)/CT scans revealed pericardial and widespread increased activity in the pleura (Figure 3). A CT scan of the abdomen revealed mild congestion in the liver. A closed pleural needle biopsy yielded reactive mesothelial cells within the fibrous material. Thus, the patient underwent a thoracoscopy. The entire parietal pleural surfaces were hyperaemic, and rare irregular thickening areas and nodules were also detected (Figure 4). As a result of the immunohistochemical analysis of the biopsy specimens, epithelial-type malignant mesothelioma was reported. Initially, the origin of the disease was the pericardial space, consequently we accepted the patient as MPeM. Following the diagnostic procedures, the patient voluntarily left the clinic. We were informed that the patient had a partial pericardectomy at another heart surgery center and died one month later.

**DISCUSSION**

MPeM is a rare type of tumor that originates from the mesothelial cells of the pericardium. Frequently, it is often diagnosed late in its course, is locally aggressive, and carries a poor prognosis (9). Although a relationship has been established with exposure to asbestos in pleural and peritoneal mesothelioma, the role of asbestos is not definite in MPeM (7). Radiation is the
most significant carcinogen for humans. It is accepted to be one of the etiologic agents for mesothelioma, with both a direct impact and a synergistic effect with asbestos. Radiation-induced tissue injury is commonly classified as acute or late effects, according to the time before appearance of symptoms. Early or acute effects emerge during or immediately after the end of therapy, while late side effects develop months to years after radiation exposure. Several biological mechanisms have been proposed to explain the late effects of radiation therapy. These include vascular injury, radiation-induced fibrogenesis, chronic oxidative stress, increased production of reactive oxygen species and free radicals, oxidation of DNA and proteins, and activation of pro-inflammatory factors (10).

Cavazza et al. reported on 8 patients who had radiotherapy for cancer and developed malignant mesothelioma within the treatment area (11). In this study, the median time between the development of malignant pleural mesothelioma and radiotherapy was reported to be 21 years. Similarly, Pappo et al. reported that malignant pleural mesothelioma developed in 3 of their patients in 11 years who underwent radiotherapy for childhood cancer within the treatment area (12). Despite these reports, Neugut et al. showed that malignant pleural mesothelioma occurred in only 2 of approximately 251,000 female patients who were administered radiotherapy for breast cancer, and also mentioned that there was no relationship between malignant pleural mesothelioma and radiotherapy (13). Only one case has been previously reported that radiotherapy for Hodgkin’s lymphoma led to the development of MPeM during the follow-up period (8). According to our patient, he had no history of environmental or occupational asbestos exposure. He was administered thoracic radiotherapy 29 years prior to diagnosis with MPeM for non-Hodgkin’s lymphoma, but then received chemotherapy (COPP) due to a relapse 5 years after the radiotherapy. A longer latent period is accepted to be characteristic of solid tumors developing secondary to radiotherapy. Another etiologic agent for this case was the use of an alkylating chemotherapeutic, such as cyclophosphamide, which is known to be carcinogenic. The synergistic effect of radiation and an alkylating agent is a potential mechanism leading to MPeM in our patient.

The onset of symptoms in MPeM is generally insidious and specious. The basis for symptoms in patients with MPeM, such as chest pain, cough, dyspnoea, and palpitations, are constrictive pericarditis developing due to the
involvement of the pericardium, and pericardial effusion, cardiac tamponade, and heart failure due to myocardial infiltration (14). The diagnosis of the disease is made as a result of the pathologic assessment of pericardial fluid or tissue generally obtained with the guidance of ECHO, ultrasonography, or CT scans. The findings detected by electrocardiogram are a decrease in QRS and T wave voltage and ST-T changes. Chest radiography of patients with MPeM typically reveals cardiomegaly, pericardial fluid findings, an irregular cardiac silhouette, or diffuse mediastinal enlargement. While an irregular, diffuse pericardial thickening and pericardial effusion is established by thoracic CT, a MRI reveals that the heart is surrounded by a pericardial mass (15).

Today, a standard treatment approach does not exist for MPeM. Although there are various studies assessing the efficiency of surgery, radiotherapy, and chemotherapy, the results are far from encouraging (7). In localized cases, surgical resection might be curative (14). Radiotherapy is not appropriate to control the disease because of such side effects as pericarditis and myocarditis. A standard chemotherapy protocol does not exist to control the disease. In recent years, anti-folate agents, such as pemetrexed, have been reported to yield successful results in patients with MPeM (16). In order to prevent pericardial tamponade or constrictive pericarditis, percutaneous balloon pericardiectomy or pericardiectomy are recommended (9). The median survival time of patients with MPeM is approximately 6-12 months (7,14).

This case shows that in patients who undergo radiotherapy to the thoracic area for cancer, development of a pericardial effusion, even after many years, requires thorough evaluation. The pericardial region must be examined, and one should not accept limited biopsies until a definitive diagnosis is made before deciding on the treatment options. In this case, opening a window from the pericardium to pleura made it possible for the tumor to pass through this window to the pleura, complicated the treatment, and probably had a negative impact on the duration of survival of the patient.

REFERENCES