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Teaching case

# Epithelioid pleural mesothelioma concurrently associated with miliary pulmonary metastases and minimal change nephrotic syndrome – A hitherto undescribed case

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ABSTRACT

Malignant pleural mesothelioma (MPM) is the aggressive disease typically spreading along the pleural surface and encasing the lung, leading to respiratory failure or cachexia. Rare cases with atypical clinical manifestation or presentation have been reported in MPM. We experienced a unique case of MPM concurrently associated with miliary pulmonary metastases and nephrotic syndrome. A 73-year-old Japanese man with past history of asbestos exposure was referred to our hospital for the investigation of the left pleural effusion. Chest computed tomography showed thickening of the left parietal pleura. Biopsy specimen of the pleura showed proliferating epithelioid tumor cells, leading to the pathological diagnosis of epithelioid MPM with the aid of immunohistochemistry. After the diagnosis of MPM, chemotherapy was performed without effect. Soon after the clinical diagnosis of progressive disease with skull metastasis, edema and weight gain appeared. Laboratory data met the criteria of nephrotic syndrome, and renal biopsy with electron microscopic examination revealed the minimal change disease. Steroid therapy was started but showed no effect. Around the same time of onset of nephrotic syndrome, multiple miliary lung nodules appeared on chest CT. Transbronchial biopsy specimen of the nodules showed the metastatic MPM in the lung. The patient died because of the worsening of the general condition. To our knowledge, this is the first case of MPM concurrently associated with multiple miliary pulmonary metastases and nephrotic syndrome.



## Introduction

Malignant mesotheliomas are rare but now increasing in number, especially in Japan [1]. Malignant mesothelioma arises from serous surface located in the pleura, peritoneum, pericardium and tunica vaginalis testis. The majority (~70%) of mesotheliomas occur in the pleura, and occupational asbestos exposure is a major cause [2]. The prognosis of malignant pleural mesothelioma (MPM) is quite poor, and the 6-month, 1-year and 5-year overall survival rates are 55, 33 and 5%, respectively [3]. The diagnosis of mesothelioma strictly depends on the pathological examination with the aid of immunohistochemical analyses, and it is generally classified into epithelioid, sarcomatoid, and biphasic types, each of which can be subdivided further [4]. In sarcomatoid mesotheliomas, the pathological differential diagnosis is sometimes quite difficult [5].

MPM typically spreads through the pleural cavity, encases the lung and directly invades adjacent tissues. The patients with MPM often show respiratory failure due to incomplete expansion of the lung and accompanying pneumonia, and finally die. However, there are some cases with atypical manifestations or presentations in MPM. For instance, miliary spread of MPM can occur in the lungs [1]. In the English literature, 12 cases of MPM with miliary pulmonary metastases or so-called "miliary mesothelioma" have been reported [6–16]. In another instance, nephrotic syndrome sometimes appears in the clinical course of MPM as a paraneoplastic syndrome [17]. In MPM, 9 cases with nephrotic syndrome have been reported in the English literature [18–26]. To the best of our knowledge, however, there was no report of mesothelioma concurrently associated with both miliary pulmonary metastases and nephrotic syndrome. We present here such an extremely rare case

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of MPM with miliary pulmonary metastases and minimal change disease (MCD) of nephrotic syndrome both of which are pathologically proven.

## Case report

A 73-year-old Japanese man with no smoking history was referred to Hyogo College of Medicine for the investigation of left pleural effusion 17 months before death. He had a past history of working at an asbestos factory for about 2 months at the age of 20. Laboratory findings on admission were unremarkable except for high concentration of hyaluronic acid in left pleural effusion (867,000 ng/ml). Tumor markers, such as carcinoembryonic antigen, cytokeratin 19 fragment, progastrin releasing peptide and tissue polypeptide antigen were all within normal range. Chest X-ray and chest computed tomography (CT) showed the left pleural effusion, thickening of the right pleura and diffuse thickening of the left pleura (Fig. 1A and B). Positron emission tomography with [F-18]-fluorodeoxyglucose (18-FDG-PET) associated with CT revealed the diffuse uptake of 18-FDG along the thickened left pleura (Fig. 1C & 1D). As shown in Fig. 2A, thoracoscopy indicated multiple nodules along the left pleura. For the definite diagnosis, biopsy of the left pleura was performed on video-assisted thoracoscopic surgery. The specimen revealed epithelioid tumor cells proliferating and invading in the fibrous tissue (Fig. 2B). These tumor cells were positive for pankeratin AE1/AE3, calretinin (Fig. 2C), D2-40 (Fig. 2D) and WT-1, and negative for TTF-1 and CEA. Thus, the pathological diagnosis of epithelioid MPM was made. Eight cycles of chemotherapy combining cisplatin (100 mg/body) and pemetrexed (750 mg/body) were done. The chemotherapy was stopped due to the progression of the bilateral pleural thickening. Then, histone deacetylase inhibitor (MK0683) had been administered for 3 months as a clinical trial. Since occurrence of the skull metastasis revealed progressive disease, the histone deacetylase inhibitor was abandoned. Approximately 4 months before his death, generalized edema and weight gain (about 10 kg within a month) appeared. Laboratory data including proteinuria (12.2 g/day), hypoalbuminemia (1.3 g/dl) and hypercholesterolemia (388 mg/dl) in addition to peripheral edema met the criteria of nephrotic syndrome [27]. Changes of urine total protein and serum albumin are shown in Fig. 3A and B. Renal biopsy was done approximately 3 month before his death. Although light microscopic examination of the specimen showed no obvious glomerular abnormality (Fig. 3C), electron microscopic examination revealed extensive foot process fusion (Fig. 3D) resulting in the diagnosis of MCD. Steroid pulse therapy (500 mg/day of methylprednisolone for 3 days) followed by oral prednisolone administration (starting dose; 50 mg/day) was performed but proved to be ineffective. Around the same time as nephrotic syndrome appeared, bilateral miliary pulmonary nodules became obvious on follow-up radiological examination without significant changes of respiratory symptoms (Fig. 4A and B). On chest CT, multiple small lung nodules were randomly distributed unrelated to lobular structure with marked thickening of pleurae. The radiological findings strongly suggested multiple hematogenous metastases of MPM in both lungs as described [28]. For the definite diagnosis, transbronchial lung biopsy was performed. On the low power view of the histological sample, nodules up to 1 mm in diameter were observed (Fig. 4C). Each of the nodules was consisted of epithelioid tumor cells (Fig. 4D) positive for pankeratin AE1/AE3, calretinin (Fig. 4E), D-20 and WT-1, and negative for CEA and TTF-1. Thus, pathological diagnosis of multiple small metastatic foci of MPM in the lungs was established. His renal function was worsened further, and the extra-corporeal ultrafiltration method and hemodialysis were applied. Gemcitabine was used as the third line chemotherapy approximately 1 month before his death, but was stopped due to pancytopenia. His general condition was deteriorated and he died 17 months after the diagnosis of MPM. An autopsy was not done because of the disagreement of the bereaved.

## Discussion

MPM typically proliferates along the pleural surface, makes thick rind around the lung and invades the adjacent tissues. Distant or multiple metastases may occur but usually in the late stage of the disease. As an unusual situation, miliary lung metastases or interstitial lung disease-like metastases may rarely develop in the course of the disease [1,29]. To the best of our knowledge, only 12 cases have been reported as mesothelioma with miliary pulmonary metastases (so-called “miliary mesothelioma”) in the English literature as shown in Table 1. Distinctively, all cases belong to the types with epithelioid component. Purek et al. reported two cases of miliary mesothelioma in residual lung on progression after the multimodal therapy [14]. In contrast, such radiographic findings seem to appear even before the diagnosis of mesothelioma [6,9,11,15,16]. Our case showed radiologic findings of “miliary mesothelioma” at the time of the evaluation of progressive disease after chemotherapy.

Glomerular diseases may occur during the course of malignant tumors as chemotherapy-induced disorder or idiopathic condition. Moreover, it is well-known that nephrotic syndrome could be induced as paraneoplastic syndrome [17]. Membranous nephropathy (MN) appears to be the most frequent glomerulopathy associated with various solid tumors [17]. On the other hand, lung cancers, colorectal cancers, renal cancers and thymomas are reported to be the solid tumors frequently associated with MCD [17]. To our knowledge, 9 cases of mesothelioma with nephrotic syndrome have been reported in the English literature as shown in Table 2. Eight of 9 cases underwent renal biopsy, and 5 were diagnosed as MCD, two as MN, and one as proliferative segmental glomerulonephritis. Our case showed typical MCD by electron microscopic examination. Thus, MCD is considered to be the most common type of nephrotic syndrome associated with mesothelioma. However, precise mechanisms why MCD is frequent in mesothelioma cases and why MN is common in other types of solid tumors are unknown. Sakamoto et al. reported a MPM case showing MN-like histological change, but their case did not meet the criteria of nephrotic syndrome [30]. In addition, a case of mesothelioma associated with IgA nephropathy was reported, but their case did not show nephrotic syndrome [31]. Association between tumor types and glomerulopathy subtypes has to be clarified in more such cases.

Taniguchi et al. reported a single case of rectal cancer with MCD and elevated vascular endothelial growth factor (VEGF). In that case, tumor removal resulted in decrease of VEGF and remission of MCD, suggesting that the elevated VEGF might be a cause of MCD in the case [32]. The most common glomerular lesion is MCD in lymphomas including Hodgkin lymphoma [17]. Nakayama et al. suggested the possible role of the inflammatory cytokines such as tumor necrosis factor-$\alpha$ in MCD preceding Hodgkin lymphoma [33]. It has also been reported that inflammatory response induced by Th2-related cytokines such as interleukin-13 (IL-13) might be important for development of MCD in patients with Hodgkin lymphoma [34]. MCD-like nephropathy has been observed to be induced by overexpression of IL-13 in rat model [35]. Although specific bioactive substances such as cytokines and growth factors were not detected in the clinical course of our case, some undetected factor might be associated with the present MCD. There is a possibility that the glomerular disease in this case may be influenced by the condition of “miliary mesothelioma” through the undetected factor.