An Autopsy Case of Malignant Pleural Mesothelioma Associated with Nephrotic Syndrome

Seiichiro Suzuki¹, Mikio Toyoshima¹, Fumiya Nihashi¹, Hiroe Tsukui², Satoshi Baba², Haruhiko Sugimura³ and Takafumi Suda⁴

Abstract

A 64-year-old man who had been exposed to asbestos was referred to our hospital for a detailed examination of left pleural effusion. A laboratory examination of the urine and blood revealed nephrotic syndrome. A thoroscopic examination did not yield a definitive diagnosis. Twenty months later, a left pleural tumor became apparent, and the patient died of respiratory failure and cachexia. An autopsy revealed epithelioid malignant pleural mesothelioma. The glomeruli appeared normal under light microscopy. A review of the English literature revealed only three reports of malignant mesothelioma associated with minimal-change nephrotic syndrome. The natural course of malignant mesothelioma with nephrotic syndrome has not been previously reported.

Key words: malignant mesothelioma, minimal-change nephrotic syndrome, paraneoplastic syndrome

(Intern Med 53: 243-246, 2014)

(DOI: 10.2169/internalmedicine.53.1313)

Introduction

Malignant mesothelioma is an asbestos-associated neoplasm of serous membranes, such as the pleura and peritoneum. In contrast to primary lung cancer (1), information regarding paraneoplastic syndromes associated with malignant mesothelioma is limited (2). We herein describe an autopsy case of malignant pleural mesothelioma associated with nephrotic syndrome and discuss possible correlations between malignant mesothelioma and nephrotic syndrome with a review of the English literature.

Case Report

A 64-year-old man was referred to our hospital for a detailed examination of left pleural effusion detected on chest radiography as part of a mass screening examination. He was asymptomatic; however, he had a 40-pack-year history of smoking. He had also worked at an asbestos products manufacturer for 10 years during his thirties and had been

exposed to asbestos fibers. His personal history included multiple brain infarctions and mild dementia. A physical examination revealed pitting edema in both legs, which had appeared two months prior to presentation at our hospital. His body weight had increased from 59.4 kg to 62.0 kg during those two months. The laboratory data showed normal urine sediment with no evidence of casts in addition to positive urine protein (9.7 g/day), hypoproteinemia (serum total protein, 5.0 g/dL), hypoalbuminemia (serum albumin, 1.9 g/dL) and hyperlipidemia (total cholesterol, 275 mg/dL), suggesting nephrotic syndrome. His renal function was normal (blood urea nitrogen, 18 mg/dL; and serum creatinine, 1.0 mg/dL). Additional laboratory studies revealed normal levels of C3 and C4 with no evidence of rheumatoid factor. No antibodies against double-stranded DNA, antinuclear antibodies, antineutrophil cytoplasmic autoantibodies or anti-glomerular basement membrane antibodies were detected. Serum protein electrophoresis and immunoglobulin (Ig) bands on immunoelectrophoresis were normal. The serum levels of IgA and IgM were within the normal limits, while the IgG levels were depressed (795 mg/dL). Negative results

¹Department of Respiratory Medicine, Hamamatsu Rosai Hospital, Japan, ²Department of Diagnostic Pathology, Hamamatsu University School of Medicine, Japan, ³Department of Tumor Pathology, Hamamatsu University School of Medicine, Japan and ⁴The Second Department of Internal Medicine, Hamamatsu University School of Medicine, Japan

Received for publication July 6, 2013; Accepted for publication September 2, 2013

Correspondence to Dr. Mikio Toyoshima, mi-toyoshima@hamamatsuh.rofuku.go.jp

Figure 1. Chest radiography (A) and computed tomography of the chest (B, C) performed on the first admission showing left massive pleural effusion. No pleural tumors, pulmonary nodules or hilar or mediastinal lymphadenopathy are evident.

were obtained for urinary light-chain excretion. Radiography and computed tomography of the chest showed left massive effusion (Fig. 1A-C). The pleural fluid contained cloudy exudate with an elevated level of hyaluronic acid (171,000 ng/mL) and no malignant cells. No microorganisms were detected in the pleural fluid. A thoracoscopic examination was performed under suspicion of malignant pleural mesothelioma. However, a macroscopic examination of the left thorax revealed no abnormalities, and a pleural biopsy did not yield a definitive diagnosis. The patient declined further examinations due to his impaired performance status resulting from multiple brain infarctions and dementia. After undergoing pleurodesis, he was followed up with supportive care as well as the prescription of a diuretic and anticoagulant for nephrotic syndrome by a local general physician. The edema persisted without any thrombosis. However, the patient began to complain of left chest pain and loss of appetite 20 months later and was again referred to our hospital. Radiography and computed tomography of the chest revealed a left pleural tumor, and computed tomography of the abdomen demonstrated left adrenal metastasis and peritoneal dissemination (Fig. 2A-C). The laboratory data disclosed positive urine protein (3.7 g/day) with normal urine sediment, hypoproteinemia (serum total protein, 5.6 g/dL), hypoalbuminemia (serum albumin, 1.3 g/dL) and mild dehydration (blood urea nitrogen, 29 mg/dL; serum creatinine, 1.1 mg/dL). Palliative treatment was administered due to the patient's rapidly worsening respiratory and general condition. He died of respiratory failure and cachexia on hospital day 11.

An autopsy revealed a left pleural tumor that had metasta-

sized to the lung parenchyma, hilar lymph nodes, liver, left adrenal gland, multiple bones and peritoneum. A microscopic examination of the pleural tumor showed epithelioid tumor cells (Fig. 3A) that were immunohistochemically positive for calretinin, D2-40 and cytokeratin (CK) 5/6 (Fig. 3B-D) and negative for carcinoembryonic antigen and thyroid transcription factor 1. Immunohistochemical staining confirmed the diagnosis of epithelioid pleural mesothelioma. Light microscopic findings of the glomeruli and uriniferous tubules were normal. Taken together with the laboratory findings, a diagnosis of minimal-change nephrotic syndrome was considered, although no electron microscopic studies were performed.

Discussion

Malignant mesothelioma cells are potent sources of various cytokines, some of which are involved in the aggressive growth and spread of malignant mesothelioma. These cytokines are also thought to be involved in various paraneoplastic syndromes, including immunosuppression, thrombocytosis, amyloidosis and hypoglycemia (2).

In the present case, whether malignant mesothelioma was involved in the development of nephrotic syndrome remains unclear. However, a review of the English literature identified seven reported cases of malignant mesothelioma associated with nephrotic syndrome (3-9). Among these seven cases, the primary site of mesothelioma was the pleura in five cases, peritoneum in one case and tunica vaginalis testis in one case. The histological type in the five reported cases of pleural mesothelioma was epithelioid in three cases, sar-

Figure 2. Chest radiography (A) and computed tomography of the chest (B) and abdomen (C) performed on the second admission showing a left pleural tumor, right pleural effusion (likely due to nephrotic syndrome), ascites and left adrenal metastasis.

Figure 3. Autopsy specimen of the pleural tumor showing epithelioid mesothelioma cells (A, Hematoxylin and Eosin staining, 200×) that are immunohistochemically positive for calretinin (B), D2-40 (C) and CK5/6 (D).

comatoid in one case and not described in the remaining case. The histological type in the reported cases of peritoneal mesothelioma and mesothelioma of the tunica vaginalis testes was epithelioid. The histological findings of the

glomeruli showed minimal changes in three of the seven cases, membranous nephropathy in two cases and mesangial proliferative glomerulonephritis in one case, with no examinations performed in the remaining case. The temporal asso-

ciation between malignant mesothelioma and nephrotic syndrome was concurrent in six of the seven cases, with malignant mesothelioma preceding the onset of minimal-change nephrotic syndrome by 11 months in one case. Solid tumors, such as lung cancer and colon cancer, are considered to be responsible for 5-10% of cases of membranous nephropathy in adults (9). Malignancy associated with membranous nephropathy may occur 12-18 months before, simultaneously with or 12-18 months after the manifestations of membranous glomerulopathy first appear (6). In the present case, malignant pleural mesothelioma became apparent and was diagnosed 20 months after the initial presentation. However, we believe that our patient had subclinical malignant mesothelioma that was not macroscopically detectable on the initial presentation.

Tumor antigens are presumably deposited in the glomeruli, followed by antibody deposition and complement activation, thus leading to epithelial cell and basement membrane injury and proteinuria due to the associated increase in glomerular permeability (6). In contrast with paraneoplastic membranous nephropathy, minimal-change glomerular disease is the most common glomerulopathy associated with lymphoproliferative malignancies, such as Hodgkin's disease, and is thought to be a disorder of the T-cell function (3). Lymphocytes obtained from patients with minimal-change nephrotic syndrome yield cytokines that can increase capillary permeability (10). Based on these previous reports, we speculate that malignant mesothelioma cell-derived cytokines, such as vascular endothelial growth factor, may play a role in the development of minimal-change nephrotic syndrome in patients with malignant mesothelioma. To clarify this hypothesis, further investigations involving a large number of patients are needed.

In conclusion, we herein reported an autopsy case of malignant pleural mesothelioma associated with minimal-

change nephrotic syndrome. We were able to observe the natural course of malignant pleural mesothelioma associated with nephrotic syndrome due to the patient's impaired performance status. A review of the English literature on nephrotic syndrome as a paraneoplastic syndrome associated with malignant mesothelioma suggested a possible correlation between malignant mesothelioma and minimal-change nephrotic syndrome.

The authors state that they have no Conflict of Interest (COI).

References

1. Yeung SC, Habra MA, Thosani SM. Lung cancer-induced paraneoplastic syndrome. *Curr Opin Pulm Med* **17**: 260-268, 2011.
2. Fitzpatrick DR, Peroni DJ, Bielefeldt-Ohmann H. The role of growth factor and cytokines in the tumorigenesis and immunobiology of malignant mesothelioma. *Am J Respir Cell Mol Biol* **12**: 455-460, 1995.
3. Schroeter NJ, Rushing DA, Parker JP, Beltaos E. Minimal-change nephrotic syndrome associate with malignant mesothelioma. *Arch Intern Med* **14**: 1834-1866, 1986.
4. Tanaka S, Oda H, Satta H, et al. Nephrotic syndrome associated with malignant mesothelioma. *Nephron* **67**: 510-511, 1994.
5. Galesic K, Bozic B, Heinzl R, Scukanec-Spoljar M, Bozikov V. Pleural mesothelioma and membranous nephropathy. *Nephron* **84**: 71-74, 2000.
6. Farmer CK, Goldsmith DJ. Nephrotic syndrome and mesenteric infarction secondary to metastatic mesothelioma. *Postgrad Med J* **77**: 333-334, 2001.
7. Bacchetta J, Ranchère D, Dijoud F, Droz JP. Mesothelioma of the testis and nephrotic syndrome: a case report. *J Med Case Rep* **3**: 7248, 2009.
8. Dogan M, Ozal G, Savas B, et al. Malign peritoneal mesothelioma with nephrotic syndrome. *Bratisl Lek Listy* **113**: 43-45, 2012.
9. Burstein DM, Korbet SM, Schwartz MM. Membranous glomerulonephritis and Malignancy. *Am J Kidney Dis* **22**: 5-10, 1993.
10. Jaurand MC, Fleury-Feith J. Pathogenesis of malignant pleural mesothelioma. *Respirology* **10**: 2-8, 2005.