CASE REPORT

Minimal change disease associated with malignant pleural mesothelioma: case report and review of the literature

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SUMMARY

A 77-year-old man with a history of asbestos exposure was admitted to our internal medicine division for generalised weakness, fatigue, loss of weight, night sweats and difficulty for breathing since 3 months. Clinical examination revealed left fine crackles and bilateral leg oedema. Blood test showed elevated C reactive protein level at 142 mg/L, lactate dehydrogenase level at 421 UI, creatinine level at 5.75 mg/dL. Serum albumin level at 30 g/L, urinalysis showed significant proteinuria at 6.4 g/L. Chest X-ray showed left pleural effusion. Renal ultrasonography was normal. Thoracic CT and positron emission tomography showed mediastinal enlargement with lymphadenopathies and left pleural effusion and thickening. A pleural biopsy showed features compatible with malignant epithelioid mesothelioma. Renal biopsy showed minimal change disease and acute tubular necrosis. A diagnosis of malignant mesothelioma associated with minimal change disease and acute tubular necrosis secondary was then made. Given the poor general condition, palliative care was initiated and the patient died from respiratory failure 3 months later.

BACKGROUND

Malignant mesothelioma is associated with asbestos exposure. Even though the use of asbestos was forbidden many years ago, new cases continue to appear due to the latency of the disease. Clinical manifestations include dyspnoea, chest pain, irritative cough and spontaneous pneumothorax. Minimal change disease (MCD) as a paraneoplastic syndrome is rare.^{1–5} We report here a new case of MCD associated with malignant pleural mesothelioma (MPM).

CASE PRESENTATION

A 77-year-old man was referred to our internal medicine division for generalised weakness, fatigue, loss of weight (10 kg), night sweats and difficulty for breathing since 3 months. He was a construction worker prior to 1980s and had been exposed to construction product which contained asbestos. He did not have any relevant medical history and was not taking any medication. Physical examination revealed a frail elderly man with 37.5°C of temperature, blood pressure 165/70 mm Hg, pulse 105 bpm, respiratory rate 22 breaths per minute with an oxygen saturation of 84% on room air. He weighed 58 kg, with a height of 168 cm, and body mass index of 20.5. Left fine crackles were heard

on auscultation. Bilateral leg oedema was present. Blood test showed elevated C reactive protein level at 142 mg/L (normal value (NV) <5 mg/L), lactate dehydrogenase level at 421 (NV <250 U/L), urea level at 80 (NV 15–50 mg/dL), serum creatinine level at 5.75 (NV 0.6–1.3 mg/dL), with estimated glomerular filtration rate (eGFR) 10 mL/min/1.73 m². Platelet count was at 253 000/μL (NV 150–350 000), neutrophil count at 6770/μL (NV 1600–7000) and serum albumin level at 30 g/L (NV 36–52 g/L). Natrium, kalium and calcium levels were normal as were liver enzymes and coagulation parameters. Urinalysis showed significant proteinuria at 6.4 g/L and urinary protein-to-creatinine ratio of 810.13 mg/mmol (urinalysis was normal 6 months ago). Chest X-ray showed left pleural effusion. Renal ultrasonography was normal. Serum protein electrophoresis was normal. Antinuclear antibodies, rheumatoid factor and anti-neutrophil cytoplasmic antibodies were negative and C3, C4 and ACE levels were normal. Thoracic CT scan demonstrated mediastinal enlargement with lymphadenopathies and left pleural effusion and thickening (figure 1A, B). Positron emission tomography showed (figure 1C, D) abnormal hypermetabolism of the left pleura as well as mediastinal, aortopulmonary window and subcarinal lymphadenopathies. Serum tumour markers like CEA, CYFRA21.1 and NSE were negative. We tried thoracentesis of the pleural effusion guided by ultrasound but the amount of liquid was too small and no puncture was performed. A lymph node biopsy was performed by endobronchial ultrasound and showed that it was reactional and not due to mesothelioma. A blinded biopsy of the pleural thickening was performed and showed tumour cells which were positive for WT1, EMA, calretinin and negative for CEA and TTF-1 on immunohistochemical analysis (figure 2A–D). Renal biopsy (figure 2E, F) shows acute tubular necrosis, no glomerular lesions on light microscopy, negative staining on immunofluorescence microscopy and no electron-dense deposits on electron microscopy. A diagnosis of malignant epithelioid mesothelioma with MCD and acute tubular necrosis secondary associated with MPM was retained.

OUTCOME AND FOLLOW-UP

Given the poor general condition, the Karnofsky performance status at 40 and nutritional state and end-stage renal failure, palliative care was deemed to be the most appropriate. However, as acute

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Figure 1 (A) Transaxial CT soft tissue window showing multiple mediastinal lymphadenopathies in station 4R and AP window (white stars). (B) Coronal CT lung window showing diffuse left pleural thickening with a patchy nodular pattern (black stars). (C) Transaxial fusion PET/CT demonstrating moderate and abnormal hypermetabolism of lymphadenopathies in station 4R and AP window (white stars). (D) Coronal FDG PET/CT fusion showing an abnormal, diffusely increased and heterogeneous fludeoxyglucose uptake of the left pleura, including within the pleural nodular thickening (black stars). AP, aortopulmonary; PET, positron emission tomography.

Figure 2 (A) Pleural biopsy. H&E staining showing clear cell change in solid pattern of epithelioid mesothelioma (black arrow). (B–D) Tumorous cells were immunohistochemically positive for WT1 ((B), nuclear positivity, black arrow); EMA ((C), membranous positivity, black arrow) and calretinin ((D), cytoplasmic and nuclear positivity, black arrow). (E) (H&E staining), (F) (periodic acid Schiff staining): kidney biopsy showing acute tubular necrosis (black arrow) and preserved glomeruli (asterisk).

tubular necrosis was present on biopsy, therapy with intravenous methylprednisolone (20 mg/kg per day for 3 days) followed by a tapering oral dose was given. After 1 month, the proteinuria significantly decreased to 1.8 g/day, creatinine level was 1 mg/dL and eGFR 60 mL/min/1.73 m² but the situation subsequently worsened, proteinuria level rose to 4 g/day and creatinine level was 3mg/dL. The patient died from respiratory failure 3 months after admission.

DISCUSSION

Malignant mesothelioma cells are sources of cytokines, antibodies which can be involved in the development of paraneoplastic syndromes. Neutrophilia, thrombocytosis, thrombophilia,⁶ a syndrome of inappropriate antidiuretic hormone production,⁷ the antiphospholipid syndrome,⁸ subacute cerebellar

degeneration,⁹ sensorimotor polyneuropathy and glomerular disease have been reported.¹⁰ MCD is the most common glomerulopathy associated with lymphoproliferative malignancies (lymphoma, leukaemia),¹¹ in contrast with membranous nephropathy which is much described with solid tumour like lung and colon cancer.¹² Glomerulopathy in the context of MPM is unusual and only 11 cases have been reported so far.^{1–5 13–18} The main characteristics of these patients are shown in table 1. The physiopathology of this association remains unknown. However, it is speculated that malignant mesothelioma cell-produced cytokines like vascular endothelial growth factor which can play a role in the development of glomerulopathy.⁴

Until now, three membranous nephropathy, two focal and segmental glomerulonephritis, one IgA nephropathy and five MCD

Table 1 Characteristics of patients with malignant pleural mesothelioma and glomerulopathy.

Author (reference number)	Age/sex	Creatinine level (mg/dL)	Proteinuria (g/day)	Type of glomerulopathy	Therapy for glomerulopathy	Therapy for mesothelioma	Evolution
Schroeter <i>et al</i> ¹	68/M	1.5	8.4	Minimal change disease	Prednisolone and cyclophosphamide	Chemotherapy	Died after 12 months
Venzano <i>et al</i> ¹³	48/M	1	>3	Membranous glomerulopathy	Prednisolone	NA	NA
Absy <i>et al</i> ¹⁴	55/M	1.57	8.8	Segmental and focal glomerulosclerosis	Prednisolone	No treatment	Died after 12 months
Tanaka <i>et al</i> ¹⁵	77/M	1	13.5	Segmental glomerulosclerosis	Prednisolone	No treatment	Died after 5 months
Galesic <i>et al</i> ¹⁶	67/M	2.73	30	Membranous glomerulopathy	Prednisolone	No treatment	Died after 11 months
Sakamoto <i>et al</i> ¹⁷	52/M	NA	4.2	Membranous glomerulopathy	No treatment	Left extrapleural pneumonectomy	Died after 12 months
Farmer and Goldsmith ²	66/M	1.15	30	Minimal change disease	Prednisolone	No treatment	Died after 7 days
Li Jy <i>et al</i> ³	58/M	3.30	>3	Minimal change disease	No treatment	Chemotherapy	Died after 2 months
Fawole <i>et al</i> ¹⁸	65/M	2.9	<3	IgA glomerulopathy	Prednisolone and cyclophosphamide	Chemotherapy	Died after 9 months
Suzuki S ⁴	64/M	1.1	3.7	Minimal change disease	No treatment	No treatment	Died after 11 days
Tsukamoto <i>et al</i> ⁵	73/M	1.1	12.2	Minimal change disease	Prednisolone	Chemotherapy	Died after 17 months
Our case	77/M	5.75	6.4	Minimal change disease	Prednisolone	No treatment	Died after 3 months

M, male; NA, not available.

have been described. All patients were men (100%). Their mean age was 63 years. The proteinuria level was in the nephrotic range (>3 g/day) in 10 of 11 patients (90%). The mean creatinine level was 1.73 mg/dL. The survival rate was 245.1 days (8 months) which is shorter than in patients with MPM without kidney disease (median survival rate 9–15 months).¹⁹ The onset of a kidney disease seems to be associated with poor prognosis.

Our case is the sixth case of MCD associated with MPM and the second case of acute tubular necrosis in the context of nephrotic syndrome associated to MPM. The findings of acute tubular necrosis are well described with MCD and involves renal function that can be recovered if steroids treatment is given rapidly. So, physicians can expect an improvement of kidney function which can allow them to prescribe chemotherapy.

Treatment of MCD classically consists of prednisolone (1 mg/kg). The remission rate is 80–90% and other immunosuppressive agents like cyclophosphamide, cyclosporine or tacrolimus are rarely necessary.²⁰ However, when MCD is secondary to a paraneoplastic syndrome, treatment of neoplasia must also be considered. In fact, Kofman *et al*²¹ showed that in patients with MCD in the context of non-Hodgkin lymphoma, relapse of MCD were more frequently present in patients treated only with steroids (77.8%) compared with those receiving steroids and chemotherapy (25%).

In most of the cases, nephrotic syndrome preceded (within 6 months) or occurred close to the time of cancer diagnosis. The diagnosis of paraneoplastic nephrotic syndrome can be considered if the following criteria are present: (1) no evidence of any other aetiology, (2) nephrotic syndrome develops 6 months before or after cancer diagnosis, (3) cancer treatment is associated with a decrease in proteinuria, and (4) cancer relapse is associated with an increase in proteinuria. In our case, the first two criteria were fulfilled but since we decide to not perform chemotherapy, the last two criteria were not relevant. The question of whether this association was coincidental or

causally related remains speculative. However, the failure of response to steroids therapy is in favour of a paraneoplastic syndrome since a remission is obtained in over 80% of nephrotic syndrome secondary to MCD.

Learning points

- ▶ Glomerular disease in the context of malignancy is well known for several decades. Most of the time, the glomerular pathology is membranous nephropathy.
- ▶ Minimal change disease (MCD) has also been described with lymphoma and leukaemia. We described here a case of MCD associated with malignant pleural mesothelioma. Only few case reports have been described so far in the literature.^{1–5}
- ▶ When MCD is secondary to a paraneoplastic syndrome, treatment of neoplasia must also be considered

Contributors HY and JCY provided clinical care to the patient and contributed equally to the writing of this paper. DH helped to analyse the anatomopathological features of kidney and pleural biopsies. SIA helped to analyse the CT and PET-CT scans. All the authors have seen and approved the final version. HY accepts responsibility for the overall content as a guarantor.

Competing interests None declared.

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