Concomitant Nephrotic Syndrome and Cryoglobulinemia in a Case of Malignant Mesothelioma

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Malignant mesothelioma is rarely associated with nephrotic syndrome. Cryoglobulinemia is found in various pathological statuses, such as hepatitis C virus infection but rarely in malignant neoplasms. We recently encountered a patient with malignant mesothelioma coincident with nephrotic syndrome and cryoglobulinemia in the course of chemotherapy. A 60-year-old man employed as a building painter was diagnosed with malignant mesothelioma by lung biopsy two years earlier and was started on chemotherapy. Nivolumab seemed effective in controlling mesothelioma, but skin immune-related adverse events occurred during the course of treatment. After discontinuation of nivolumab and administration of gemcitabine as an alternative therapy, the patient was referred to a nephrologist because of the subsequent development of edema, renal injury, and proteinuria. Following the investigation, he was diagnosed with nephrotic syndrome and cryoglobulinemia with C4-dominant cold activation. However, a percutaneous renal biopsy could not be performed due to persistent severe cough induced by pleural involvement. The patient died a little over three years after the pathological diagnosis of pleural mesothelioma. Our case had three key features: nephrotic syndrome was possibly associated with malignant mesothelioma; cryoglobulinemia occurred in malignant mesothelioma; and concomitant nephrotic syndrome and cryoglobulinemia occurred after chemotherapy. Unfortunately, our rare case lacks a basis in renal pathology or evidence of links between the pathogenesis of malignant mesothelioma, cryoglobulinemia, and nephrotic syndrome. This case does not provide a causal mechanism, but may be worth adding to the case list as one of the rare renal involvement in a patient with malignant mesothelioma.
mesothelioma from a thoracoscopic lung biopsy 2 years earlier and was started on chemotherapy. Cisplatin plus pemetrexed (CDDP + PEM) and carboplatin plus pemetrexed (CBDCA + PEM) were determined to result in an insufficient response, and nivolumab was considered to have induced immune-related adverse events and was discontinued. After starting the administration of gemcitabine (GEM), drug-induced lung injury occurred. He was also referred to a nephrologist because of the subsequent development of edema, renal injury, and proteinuria. After investigations and careful consideration, vinorelbine (VNR) was administered to treat the nephrotic syndrome with cryoglobulinemia due to the progression of malignant mesothelioma. Response of chemotherapy to malignant mesothelioma is presented as partial response (PR), stable disease (SD), and progressive disease (PD). Palliative care was subsequently provided, along with radiation therapy for metastatic bone lesions and antibiotics against bacterial pneumonia. The patient died a little over 3 years after the pathological diagnosis of mesothelioma without recurrence of nephrotic syndrome in the end-stage of cancer.

Figure 1: The clinical course of the patient. Two years earlier, the patient had been diagnosed with malignant mesothelioma by lung biopsy and treated with chemotherapy. Cisplatin plus pemetrexed (CDDP + PEM) and carboplatin plus pemetrexed (CBDCA + PEM) were determined to result in an insufficient response, and nivolumab was considered to have induced immune-related adverse events and was discontinued. After starting the administration of gemcitabine (GEM), drug-induced lung injury occurred. He was also referred to a nephrologist because of the subsequent development of edema, renal injury, and proteinuria. After investigations and careful consideration, vinorelbine (VNR) was administered to treat the nephrotic syndrome with cryoglobulinemia due to the progression of malignant mesothelioma. Response of chemotherapy to malignant mesothelioma is presented as partial response (PR), stable disease (SD), and progressive disease (PD). Palliative care was subsequently provided, along with radiation therapy for metastatic bone lesions and antibiotics against bacterial pneumonia. The patient died a little over 3 years after the pathological diagnosis of mesothelioma without recurrence of nephrotic syndrome in the end-stage of cancer.
proteinuria had disappeared after VNR therapy. Percutaneous renal biopsy could not be performed due to persistent severe cough induced by pleural involvement. The clinical diagnosis was thought to be nephrotic syndrome with cryoglobulinemia due to the progression of malignant mesothelioma. Thereafter, palliative care was provided, along with radiotherapy for metastatic bone lesions and antibiotics against bacterial pneumonia. The patient died a little over three years after pathological diagnosis of mesothelioma without recurrence of nephrotic syndrome in the end-stage of cancer.

3. Discussion

The present case showed three features newly developed nephrotic syndrome was possibly associated with malignant mesothelioma; cryoglobulinemia occurred in malignant mesothelioma; and concomitant transient nephrotic syndrome and cryoglobulinemia occurred after the use of nivolumab or GEM, but not VNR. Unfortunately, this case lacked a basis in renal pathology or evidence of links between the pathogenesis of malignant mesothelioma, cryoglobulinemia, and nephrotic syndrome. However, we discuss here the causal relationship between the three events based on the literature as much as possible.

We reviewed 15 publications presenting cases of nephrotic syndrome with malignant mesothelioma at various sites [2–16]. Seven cases included information on complement levels, all of which were within the normal range. A description of cryoglobulins was absent in all previous cases (Table 2). Most of the renal pathology involved minimal-change disease in patients with malignant mesothelioma and nephrotic syndrome [12], accounting for 9 of the 15 cases (60%) in Table 2. Three cases of membranous nephropathy were identified, followed by one case each of focal segmental glomerulosclerosis and mesangial proliferative nephritis, but no reports of membranous proliferative glomerulonephritis, which may occur in cryoglobulinemia. Meanwhile, definitively assessing the pathological characteristics of this case is difficult because renal biopsy could not be performed at the moment of nephrotic syndrome due to the condition of the patient. Nevertheless, the result of the high selectivity of proteinuria (index, 0.09; Table 1) suggests the possibility of minimal-change disease, consistent with previous cases.

### Table 1: Laboratory findings.

| Urinalysis | Blood chemistry tests (cont.) |
|---|---|
| Gravity | Sodium 136 mmol/L |
| Protein | Chloride 104 mmol/L |
| Sugar | Potassium 3.0 mmol/L |
| Blood | Corrected calcium 10.0 mg/dL |
| Sediment | Phosphate 3.0 mg/dL |
| Red blood cells | Total bilirubin 0.3 mg/dL |
| White blood cells | Aspartate aminotransferase 22 U/L |
| Urinary biochemical tests | Lactate dehydrogenase 292 U/L |
| Daily urinary protein | Alkaline phosphatase 167 U/L |
| Selectivity index | Creatine kinase 73 U/L |
| Bence-Jones protein | Complete blood count |
| Basophils | Total cholesterol 197 mg/dL |
| Lymphocytes | Neutrophils 10600/mL |
| Monocytes | LDL cholesterol 129 mg/dL |
| Hemoglobin | Triglyceride 191 mg/dL |
| Platelets | Glucose 103 mg/dL |
| Coagulation tests | Basophils 3% |
| PT-INR | Hemoglobin A1c 5.1% |
| APTT | Selectivity index 0.09 |
| Fibrinogen | Immunoglobulin G 2288 mg/dL |
| von Willebrand factor | PT-INR 1.13 |
| Blood chemistry tests | Immunoglobulin A 455 mg/dL |
| Total protein | Immunoglobulin M 94 mg/dL |
| Albumin | Complement 3 170 mg/dL |
| Uric acid | Complement 4 17 mg/dL |
| Urea nitrogen | CH50 57.0 U/mL |
| Creatinine | Antinuclear antibody x40 |
| C-reactive protein | Anti-dsDNA-Ab < 10 U/mL |
| PR3-ANCA | ASO < 1.0 U/mL |
| MPO-ANCA | Cryoglobulin (+) |
| Coagulation tests | Rheumatoid factor 33 IU/mL |

HPE: high-power field; PT-INR: prothrombin time-international normalized ratio; APTT: activated partial thromboplastin time; CH50:50% hemolytic unit of complement; LDL: low-density lipoprotein; HBs: hepatitis B surface; HCV: hepatitis C virus; dsDNA-Ab: double-strand deoxyribonucleic acid antibody; PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibodies; MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibodies.

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Cryoglobulinemia-associated glomerulonephritis is most commonly seen in the context of hepatitis C infection and occasionally seen in relation to lymphoma and malignant neoplasm [18,20–22]. In contrast with renal disease associated with HCV, renal involvement in patients with cryoglobulinemia not associated with HCV has only been poorly described, and few cases have been reported [23]. In an analyzed series of 20 cases without HCV-associated cryoglobulinemia, renal involvement was characterized by nephrotic range proteinuria in 75% of patients and renal failure in 85% of patients (mean glomerular filtration rate, 46 mL/min/1.73 m²) [23]. Membranoproliferative glomerulonephritis with subendothelial deposits was observed in all kidney specimens [23]. Generally, therapeutic options for the disease include removal of circulating cryoglobulin by plasmapheresis, immunosuppression, and pharmacological treatment to address the underlying cause of protein production. After excluding the possibility of any infectious diseases, including viral hepatitis, and careful consideration, we tried suppression of cancer progression by next-line chemotherapy with VNR after the diagnosis of nephrotic syndrome. In this case, cryoglobulin disappeared without apheresis or immunosuppressive drugs, suggesting that one of the relevant mechanisms was anticancer therapy reducing the tumor burden as an antigen against cryoglobulin.

Another possibility for the pathogenesis was that the concomitant nephrotic syndrome and cryoglobulinemia were driven by chemotherapy. In terms of the time course, in this case, the suspect drug was nivolumab or GEM, but not VNR. Only one study suggested that anti-PD-1-related cryoglobulinemia during nivolumab treatment in a patient with lung cancer [24]. He was treated with prednisone and cryoprecipitates disappeared after 26 days of steroid therapy. The patient continued to receive nivolumab for a total of eight cycles with no recurrence of cryoglobulinemia [24]. Nivolumab is also known as a rare cause of nephrotic syndrome during cancer therapy, represented by minimal-change disease [25], membranous nephropathy [26], membranoproliferative glomerulonephritis [27], and renal vasculitis [28]. A hemolytic uremic syndrome is the most perilous adverse effect of gemcitabine, with an incidence of approximately 0.15% based on reported cases [29]. GEM-induced secondary thrombotic microangiopathy may be diagnosed as a nephrotic syndrome [30]. Membranous nephropathy as a cause of nephrotic syndrome was also found in a case treated using GEM [31]. Collectively, both nivolumab and GEM could cause nephrotic syndrome, while no previous reports have shown any association between GEM and cryoglobulinemia. Therefore, if we consider nephrotic syndrome and cryoglobulinemia to represent linked complications rather than coincidences, the suspect drug is most likely nivolumab, not GEM.

To the best of our knowledge, this represents the first description of concomitant nephrotic syndrome and cryoglobulinemia in a case of malignant mesothelioma. Although no causal mechanisms or pathological findings were identified, this case may be worth adding to the case list as a rare coincidence in a patient with malignant mesothelioma.
Data Availability

The data generated during the current case are available from the corresponding author upon reasonable request.

Conflicts of Interest

Acknowledgments

The authors declare that they have no conflicts of interest for this article. The corresponding author is employed by the University of Tsukuba.

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