Abstract:
A 68-year-old woman developed systemic blisters while receiving treatment for nephrotic syndrome. As she also developed marked liver dysfunction and disseminated intravascular coagulation, she was admitted to our hospital. She was diagnosed with varicella zoster virus (VZV) infection. Treatment was administered in the intensive-care unit, but the patient died on day 24 post-admission after severe VZV infection. A post-mortem examination showed micro-abscesses and necrosis caused by varicella zoster infection in multiple organs, including the liver, kidneys, and gastrointestinal tract. Because VZV infection can become severe in immunocompromised patients, careful consideration is needed for the prevention and treatment of the viral infection.

Key words: varicella zoster virus, nephrotic syndrome, immunosuppressive therapy

Introduction
Herpes zoster is caused by the reactivation of varicella zoster virus (VZV), which remains latent in the dorsal root ganglia. Herpes zoster is highly prevalent in Japan, with an occurrence rate of 4.15 per 1,000 individuals (1). Herpes zoster is more common in older adults than in younger ones. Those with reduced T-cell immunity (e.g. recipients of an organ transplant or hematopoietic stem cells; patients receiving immunosuppressive therapy; and those with lymphoma, leukemia, or HIV infection) are at high risk of exacerbation (2).

In general, a patient with herpes zoster infection develops blisters on one side of the body along a single nerve pathway. Disseminated herpes zoster, which is a rash with disseminated lesions, may lead to visceral complications (3). Among patients who have undergone hematopoietic stem cell transplantation, 10% of those who develop disseminated herpes zoster die (4). However, the mortality rate in those with renal disease is unknown.

We herein report a recent autopsy case of disseminated herpes zoster infection, in which the deceased patient had been receiving immunosuppressive therapy for nephrotic syndrome.

Case Report
A 68-year-old woman developed generalized blisters while receiving treatment for nephrotic syndrome. As she also developed marked liver dysfunction, renal dysfunction, and disseminated intravascular coagulation, she was admitted to our hospital as an emergency case. Three years earlier, she had shown the onset of nephrotic syndrome associated with cryoglobulinemic vasculitis and received treatment for remission with 30 mg/day of prednisolone (PSL) and cryofiltration. Thereafter, as proteinuria improved, the PSL dose was tapered to 5 mg/day, and the patient received...
Table. Laboratory Findings.

| [Blood test] | TP   | 3.4 g/dL | VZV IgG (EIA) | 55.8 |
|--------------|------|----------|---------------|------|
| WBC 6,800 /μL | Alb  | 1.6 g/dL | VZV IgM (EIA) | 0.89 |
| RBC 266×10^12 /μL | BUN | 35 mg/dL | VZV-DNA (EIA) | 4.0×10^10 copies/mL |
| Hb 8.8 g/dL | Cr   | 1.31 mg/dL |             |      |
| Hct 24 % | eGFR | 31.8 mL/min/1.73m² |       |      |
| PLT 7.7×10^11 /μL | Na  | 132 mEq/L | Protein (3+) |      |
| PT-INR 3.0 | K    | 4.7 mEq/L | Glucose (-)  |      |
| APTT 88.9 sec | Cl  | 86 mEq/L | Urobilinogen (-) | |
| FDP 177 μg/mL | Glu | 78 mg/dL | Bilirubin (-) |      |
| D-dimer 74.3 μg/mL | LDL-C | 122 mg/dL | Ketone (-) |      |
| T.Bil 1.6 mg/dL | CRP | 1.67 mg/dL | Occult blood (3+) |      |
| AST 2,670 U/L | IgG | 280 mg/dL | RBC >100 /HPF |      |
| ALT 747 U/L | IgA | 97 mg/dL | WBC 10-19 /HPF |      |
| ALP 820 U/L | C3  | 20 mg/dL |      |      |
| γGTP 257 U/L | C4  | 3.2 mg/dL |      |      |
| LDH 6,713 U/L | C  |      |      |      |
| CK 199 IU/L |      |      |      |      |

Alb: albumin, ALT: alanine transaminase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, APTT: activated partial thromboplastin time, BUN: blood urea nitrogen, Cl: chloride, Cr: creatinine, CK: creatine kinase, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, FDP: fibrin/fibrinogen degradation products, γGTP: gamma-glutamyl-transferase, Glu: glucose, Hb: hemoglobin, Hct: hematocrit, IgA: immunoglobulin A, IgG: immunoglobulin G, IgM: immunoglobulin M, K: potassium, LDL-C: low density lipoprotein Cholesterol, LDH: lactate dehydrogenase, Na: sodium, PLT: platelet, PT-INR: prothrombin time-international normalized ratio, RBC: red blood cell, T.Bil: total bilirubin, TP: total protein, VZV: varicella zoster virus, WBC: white blood cell.

maintenance therapy. Three months earlier, the patient had had recurrence of nephrotic syndrome and been admitted to the previous hospital where she received steroid pulse therapy (methylprednisolone 500 mg/day, 3 days). Thereafter, treatment with 30 mg/day of PSL and 100 mg/day of mizoribine (MZR) had been commenced.

Two days before admission to our hospital, she developed diffuse blisters on the right side of her body. Thereafter, she experienced severe acute chest pain, and the blisters spread throughout her body. The patient tested positive on the Tzanck test and was diagnosed with herpes infection. Treatment with acyclovir (ACV) 1,200 mg/day was initiated. Our hospital took over the treatment.

As described above, the patient was suspected of having herpes zoster infection. Urinalysis results indicated proteinuria (urinary plasma creatinine ratio: 6.68 g/gCr) and hematuria (>100/high-power field). Thoracoabdominal contrast-enhanced computed tomography showed an enlarged liver, spleen, and kidneys. Organ injury was observed, as indicated by inhomogeneous contrast enhancement. Pleural effusion and ascites were present, and consolidation accompanied by an air bronchogram was observed in the bilateral lower lobes (Fig. 1).

The patient was in a condition of shock with respiratory failure and disseminated intravascular coagulation. Mechanical ventilation via endotracheal intubation was initiated. In addition, as the patient developed anuric acute kidney injury, continuous hemodiafiltration was commenced, and the patient was admitted to the intensive-care unit. A bone marrow test showed marked hemophagocytic findings, which we considered to be hemophagocytic lymphohistiocytosis syndrome (HLS) accompanying severe viral infection. We continued the administration of ACV, which had been started at the previous hospital. As the patient was suspected of having pneumonia-associated sepsis, empirical treatment was also commenced with the broad-spectrum antibacterial agents meropenem and vancomycin. No additional treatments, such as immunosuppressant therapy, were provided for cryoglobulinemic vasculitis because treatment of severe infection was prioritized. MZR was discontinued, and PSL was gradually reduced and then discontinued. Following treatment initiation, the blisters crusted, but the patient’s general condition remained poor. ACV was administered at a dosage of 1,200 mg/day, but the dose was reduced to 250 mg/day due to crusting of the blisters. Pancytopenia due to HLS progressed, and the patient required red blood cell and plate-
let transfusion over the course of several days. She died on post-admission day 24 (Fig. 2).

A post-mortem examination was conducted after obtaining consent from the patient’s family. Infiltration of inflammatory cells and coagulative necrosis accompanied by intranuclear inclusion bodies were observed in the liver; findings of pulmonary edema as well as micro-abscesses, which were considered the foci of disseminated viral infection, were also observed. In addition, severe neutrophil infiltration was seen in the left pleurae, suggesting purulent pleuritis. Findings of myocardial necrosis accompanied by infiltration of inflammatory cells were observed in the heart; micro-abscesses and necrosis were also seen in the spleen and pancreas. Destructive lesions of the glomeruli accompanied by fibrin deposition and acute tubular necrosis were observed in the kidneys (Fig. 3). Furthermore, ulcers, which were considered to have been caused by viral infection, were observed in the stomach and both the ascending and descending colon. Hemophagocytosis and necrotic foci were observed in the bone marrow.

Taken together, the above findings indicated VZV infection-induced necrosis of almost all the viscera. Although VZV immunostaining was not performed, we considered these observations to be pathological findings associated with VZV infection because VZV viremia and nuclear inclusion bodies were observed. The cause of death was therefore established as multiple organ failure from disseminated herpes zoster.

**Discussion**

This patient developed disseminated herpes zoster while receiving immunosuppressive therapy for nephrotic syndrome. Her condition worsened to multiple organ failure, which led to her death. The present case suggests that VZV infection should be considered when treating a patient with

**Figure 1.** Computed tomography findings. The liver, spleen, and kidneys were found to be enlarged, and inhomogeneous contrast enhancement was seen. Pleural effusion and ascites were present, and consolidation accompanied by air bronchogram was observed in the bilateral lower lobes.

**Figure 2.** Clinical course. ACV: acyclovir, MEPM: meropenem, VCM: vancomycin, mPSL: methylprednisolone, IVIG: Intravenous immunoglobulin, WBC: white blood cell, Hb: hemoglobin, PLT: platelet, AST: aspartate aminotransferase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein, VZV: varicella zoster virus
Figure 3. Pathological anatomical findings. a) Lungs (macroscopic findings). Left lung 395 g, right lung 520 g (left is right lung). The cut surface is yellowish-brown with edema and hyperemia. Blood and fibrin retention can be observed between the lobes in the left lung (arrow). b) Lungs (microscopic findings). In the bilateral lungs, pulmonary edema was found, and the foci of fibrin precipitation and inflammatory cell infiltration were partially observed as shown in the photograph (left: ×20). Eosinophilic intranuclear inclusion bodies were observed in a small number of macrophages with halos around them (arrows, central: ×40). Multinucleated giant cells with eosinophilic intranuclear inclusion bodies were also observed (right: ×40). c) Liver (macroscopic findings). The liver weighed 785 g. Necrosis with a yellowish-brown tone was observed. d) Liver (microscopic findings). Confluent necrosis is observed, which accounts for 20%–30% of the total liver. The necrosis was surrounded by cells showing ground-glass-like nuclei (left: ×4, right: ×40). e) Spleen (macroscopic and microscopic findings). The spleen weighed 110 g. Adhesion of yellowish-brown moss-like material is observed on the film. Necrosis can be observed on the cut surface (arrow). Extensive necrosis and blistering were observed in the spleen (×20). f) Kidneys (macroscopic and microscopic findings). Left kidney 146 g, right kidney 132 g (the right kidney is shown on the left). The cortex is reddish-brown, and the medulla is greenish-brown. In the glomerulus, a crescent formation was observed. It was covered with cells showing ground-glass-like nuclei, and an inclusion body-like structure was also observed (arrow, ×40).
kidney disease who requires immunosuppressive therapy as carefully as patients with blood disorders and transplantation. This case study is novel because, to our knowledge, there have been no reports of disseminated VZV infection in patients with cryoglobulinemic vasculitis.

While the epidemiology and prognosis of disseminated herpes zoster is widely recognized in the fields of blood disease and transplantation (5, 6), it is not widely recognized in nephrology. Despite the importance of being adequately informed on herpes zoster in order to perform disease treatment, few nephrologists have sufficient knowledge (7). The onset and exacerbation of herpes zoster is associated with reduced T-cell immunity (2). When treating kidney diseases, including nephrotic syndrome and glomerulonephritis, drugs that suppress T cell immunity, such as corticosteroids, are primarily used. Therefore, treatment using such drugs may increase the risk of VZV infection. Mizoribine, an immunosuppressant, also selectively suppresses the proliferation of lymphocytes by inhibiting the purine synthesis pathway of nucleic acids. Therefore, it was considered that the drug had a negative impact on the patient’s immunity by inhibiting the proliferation of T and B cells.

We confirmed disseminated lesions caused by VZV in a post-mortem examination. There have been similar post-mortem studies on patients who died from disseminated herpes zoster infection (8-13). However, few reports on post-mortems of patients with kidney disease who died from disseminated herpes zoster infection have been published. In our patient, a pathological analysis showed VZV infection-induced micro-abscesses and necrosis in the liver, lungs, pleurae, heart, stomach, colon, kidneys, spleen, pancreas, and bone marrow. The patient’s VZV-DNA content in the blood was also extremely high. It was considered that the virus spread through the body via the bloodstream, resulting in various organ injuries. In particular, the liver was severely necrotic, which may pathologically explain the marked elevation of hepatic enzymes. Furthermore, broad necrosis was observed in the spleen. In the lungs, eosinophilic inclusion bodies were observed in a small number of macrophages with halos around them. In the kidneys, crescent formation, glomerular necrosis, and fibrin deposition were observed. Intranuclear inclusion body-like structures were also observed. These findings were therefore considered to be pathological findings related to VZV infection rather than those of cryoglobulinemic vasculitis, which was the underlying disease. The central nervous system was not evaluated in the present study. However, as the patient exhibited impaired consciousness, she might have developed VZV infection-induced encephalomyelitis and meningitis.

Among patients with herpes zoster, those who are ≤ 50 years old and have moderate to severe rash or pain, facial and ocular lesions, and acute infective complications and are immunodecient are at a high risk of exacerbation. Aggressive antiviral therapy is indicated for such patients, and it is recommended that therapy be commenced within 72 h after the onset (2). Early symptoms of disseminated herpes zoster include severe pain in the abdomen, back, and lower back caused by visceral infection. These symptoms may appear prior to rash. Given the high mortality rate, early detection is key to providing effective treatment. In the present case, the patient had severe chest pain before developing generalized blisters. The patient’s risk factors were old age and immune deficiency. In addition, treatment was commenced after more than 72 h had passed since the symptom onset. These factors were considered to be the causes of the VZV-induced progression observed in the visceral lesions.

VZV loads remained abnormally high even after ACV therapy was commenced. As ACV resistance was observed during treatment, the patient might have had ACV-resistant VZV infection. Studies have reported the effectiveness of foscarnet for ACV-resistant VZV infection, although the drug has not been approved for the treatment of herpes zoster in Japan (2, 14).

To prevent the onset and worsening of herpes zoster, vaccine inoculation against the disease is also important. At present, the available herpes zoster vaccines are recombinant zoster vaccine (RZV) and zoster vaccine live (ZVL). The Advisory Committee on Immunization Practices recommends that RZV be administered to adults ≥50 years old with normal immunocompetence, irrespective of the presence of comorbidities (15, 16). As ZVL is a live vaccine, it is, in principle, contraindicated for patients with compromised immunity. However, one study reported the safety of the live vaccine in patients with nephrotic syndrome receiving immunosuppressive therapy (17). Whether or not the patient in the present case had received a varicella vaccine was unclear. In children with steroid-sensitive nephrotic syndrome, live vaccines should be avoided if prednisone doses are 1 mg/kg daily (<20 mg/day) or 2 mg/kg every other day (<40 mg every other day), in which case corticosteroid-sparing immunosuppressive agents and varicella zoster globulin should be administered in case of contact with VZV infection for nonimmune children on immunosuppressive agents (18). No consensus has been reached concerning adult cases. When treating a patient with kidney disease, it is necessary to ask them about their vaccination history and consider inoculation against herpes zoster prior to immunosuppressive therapy.

We reported an autopsy case of disseminated herpes zoster. The patient died from the disease while receiving immunosuppressive therapy for nephrotic syndrome. Patients with severely compromised immunity, including those who have undergone hematopoietic stem cell transplantation, may develop life-threatening disseminated herpes zoster. This can also occur in immunocompromised renal disease patients. Nephrologists may often consider preventing common bacterial (e.g. Mycobacterium tuberculosis) and fungal infections, but they are rarely aware of viral infection. It is important to detect the disease at an early stage, so patients exhibiting chest or abdominal pain and presenting with blisters while receiving immunosuppressive therapy should be closely evaluated for the possibility of herpes zoster infection.
The authors state that they have no Conflict of Interest (COI).

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