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CASE REPORT

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Infection-associated hemophagocytic syndrome in a diabetic patient undergoing chronic hemodialysis

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Abstract
Hemophagocytic syndrome (HPS) is an uncommon but severe illness associated with a variety of infections, malignant tumors, and autoimmune diseases. We report a case of infection-associated HPS in a patient receiving chronic hemodialysis. *Peptostreptococcus*-induced sepsis and abscess formation in the left iliopsoas muscle led to the onset of infection-associated HPS in this patient. The patient had diabetes mellitus and end-stage renal disease, and it is likely that immunological dysfunctions from these disorders played a part in the onset of both severe bacterial infections and HPS.

Key words Infection-associated hemophagocytic syndrome · Hemodialysis · Hypercytokinemia

Introduction

Hemophagocytic syndrome (HPS) is a rare disease characterized by the systemic proliferation and activation of hemophagocytic cells. Patients with HPS clinically present with fever, pancytopenia, hepatosplenomegaly, liver dysfunction, and coagulopathy. Adult HPS is mostly secondary to viral or bacterial infections, malignant tumors, or autoimmune diseases. Infection-associated HPS has been reported with various infectious agents and sometimes occurs in patients with immunocompromised conditions. Here we report a case of infection-associated HPS with bacterial infection in a patient undergoing hemodialysis. Immunological abnormalities based on diabetes mellitus and end-stage renal disease (ESRD) were thought to play a part in the development of HPS in this patient.

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Case report

A 67-year-old man was transferred to Niigata University hospital with fever, consciousness disturbance, and pancytopenia on March 23, 2001. He had been diagnosed with ESRD caused by diabetic nephropathy, and he had started maintenance hemodialysis on April 24, 1998. Two months prior to admission to our hospital he had been admitted to another hospital with erythropoietin-resistant anemia and gastric ulcers. Severe thrombocytopenia occurred 2 weeks after the administration of famotidine, which was therefore stopped, and platelet transfusion was performed. On March 3, high fever and elevated C-reactive protein (CRP) levels were observed. Catheter infection was suspected, and so the central venous catheter was removed. A blood culture was positive for *Peptostreptococcus micros*. The fever continued despite the immediate administration of imipenem/cilastatin. A low-density mass in the left iliopsoas muscle was detected by computed tomography (Fig. 1), suggesting an abscess. Severe pancytopenia occurred when the antibiotics were changed to piperacillin and minocycline. A physical examination on admission to our hospital revealed the patient to be pale, febrile, and drowsy. There was no skin eruption, and no evidence of hemorrhagic tendency.

A laboratory investigation (Table 1) revealed pancytopenia and chronic renal failure. Hemoglobin A1c was 6.2%, and diabetes was well controlled with hyperalimentation and the continuous infusion of insulin. Transaminases and choline esterase levels were low but were considered to be within the normal ranges for dialysis patients. Fibrin degradation products and D-dimer levels were slightly elevated and antithrombin III level was low at 43%. These data, together with the finding of severe thrombocytopenia, suggested the existence of disseminated intravascular coagulation (DIC). The patient was negative for antinuclear antibodies and his clinical symptoms and labo-

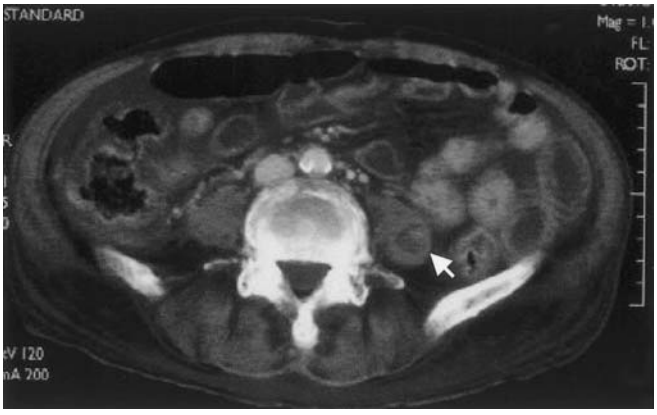

Fig. 1. Computed tomography scan. A low-density mass is evident (*arrow*) in the left iliopsoas muscle

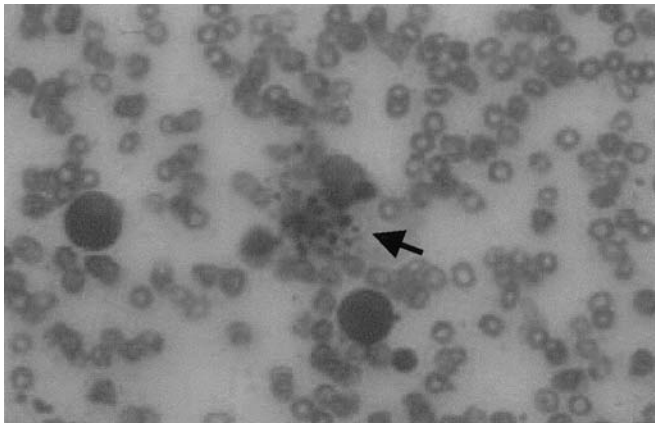

Fig. 2. Bone marrow smear. The smear reveals histiocytes with phagocytosis of platelets (*arrow*). (Wright–Giemsa stain, ×100)

Table 1. Laboratory data on admission

Blood count	Serum chemistry	
WBC 2320/mm^3	TP 5.0 g/dl	ALT 4 IU/l
RBC 205 × 10^4/mm^3	Alb 2.5 g/dl	AST 0 IU/l
Hb 6.3 g/dl	BUN 98 mg/dl	γ-GTP 31 IU/l
Ht 19.8%	Cr 10.1 mg/dl	LDH 355 IU/l
Plt 3.9 × 10^4/mm^3	UA 9.1 mg/dl	ALP 100 IU/l
Coagulation tests	NA 143 mEq/l	ChE 43 IU/l
APTT 34.1 s	K 4.5 mEq/l	CPK 10 IU/l
HPT 76%	Cl 106 mEq/l	TB 0.5 mg/dl
Fbg 364 mg/dl	Ca 8.2 mg/dl	TC 81 mg/dl
FDP 18.5 μg/ml	iP 6.3 mg/dl	TG 166 mg/dl
D-dimer 13.6 μg/ml	FBG 92 mg/dl	Hb_{A1C} 6.2%
ATIII 43%		
Immunological findings		
CRP 28.1 mg/dl	sIL2R 7668 U/ml	
IgG 1610 mg/dl	IFNγ <6 pg/ml	
IgA 110 mg/dl	IL1β <10 pg/ml	
IgM 82 mg/dl	IL4 15.9 pg/ml (normal <5.0)	
C3 36.9 mg/dl	IL6 43.1 pg/ml (normal <4.0)	
C4 17.5 mg/dl	TNF α 10 pg/ml (normal <5.0)	
CH50 23 U/ml		
ANA 14.0 index		
RF <5 IU/ml	CMV IgG (+)	
p-ANCA <10 EU/ml	CMV IgM (−)	
c-ANCA <10 EU/ml	CMV antigenemia (−)	
PAIgG 477.7 ng/10^7 cells	EBV IgG ×640	
Direct Coombs (+)	EBV IgM <×10	
Indirect Coombs (+)	EBNA ×20	
Haptoglobin 188 mg/dl	PalvoB19 IgG (−)	
Ferritin 1541 ng/ml	PalvoB19 IgM (−)	

ratory data did not fulfill the criteria of autoimmune diseases such as systemic lupus erythematosus. CRP was markedly elevated at 28.1 mg/dl. Direct and indirect Coomb's antiglobulin were both positive. Ferritin was 1541 ng/ml and soluble interleukin-2 (IL-2) receptor was 7668 U/ml. The levels of other cytokines, including IL-4, IL-6, and tumor necrosis factor-α (TNF-α), were also elevated. Bone marrow aspiration (Fig. 2) revealed severe hemophagocytosis, and hemophagocytic syndrome was diagnosed by this pathological finding.

After the antibiotics were changed to ciprofloxacin and vancomycin, the CRP level decreased to 6.9 mg/dl, but the platelet count fell to 1000/μl despite platelet transfusion and the continuous infusion of nafamostat mesilate. Intravenous high-dose immunoglobulin administration followed by steroid pulse therapy was started after the diagnosis of HPS. Pneumonia developed in the right lung after the treatment, and the patient was transferred to the intensive care unit with respiratory support. His sputum culture was positive for Methicillin-resistant *Streptococcus aureus* (MRSA) and *Serratia marcescents*. Vancomycin was effective for these two species of bacteria, and the platelet count increased to over 50 000/μl with the improvement of his pneumonia. However, fever recurred when the steroid dosage was reduced, and inflammation developed in the right parotid gland with *MRSA* being detected in the pus from the parotid gland. His platelet count fell again and liver dysfunction occurred. Chemotherapy with etoposide and cyclosporin was started on April 12, 2001. This lowered the levels of liver enzymes, but severe pancytopenia recurred and the patient died of pneumonia.

At autopsy, pneumonia in the bilateral lungs, suppurative parotitis, and necrotizing myositis of the iliopsoas muscle were seen. The bone marrow showed histiocytic proliferation with hemophagocytosis (Fig. 4). There was no evidence of malignant tumors.

Discussion

HPS is a clinicopathologic condition characterized by the systemic proliferation of benign histiocytes, fever, pancytopenia, hepatosplenomegaly, liver dysfunction, and coagulopathy.[1] HPS in adults is often associated with malignant lymphoma, autoimmune diseases, and viral or bacterial infections. Infection-associated HPS has been reported with various infectious agents, including the Epstein–Barr virus, cytomegalovirus, gram-negative bacteria, tuberculosis, and fungi.[2–6] It sometimes occurs in patients in immunocompromised conditions, such as when using steroids or immunosuppressants.

The mechanisms of HPS are still unknown. In Epstein–Barr virus-associated HPS, infection of T lymphocytes is

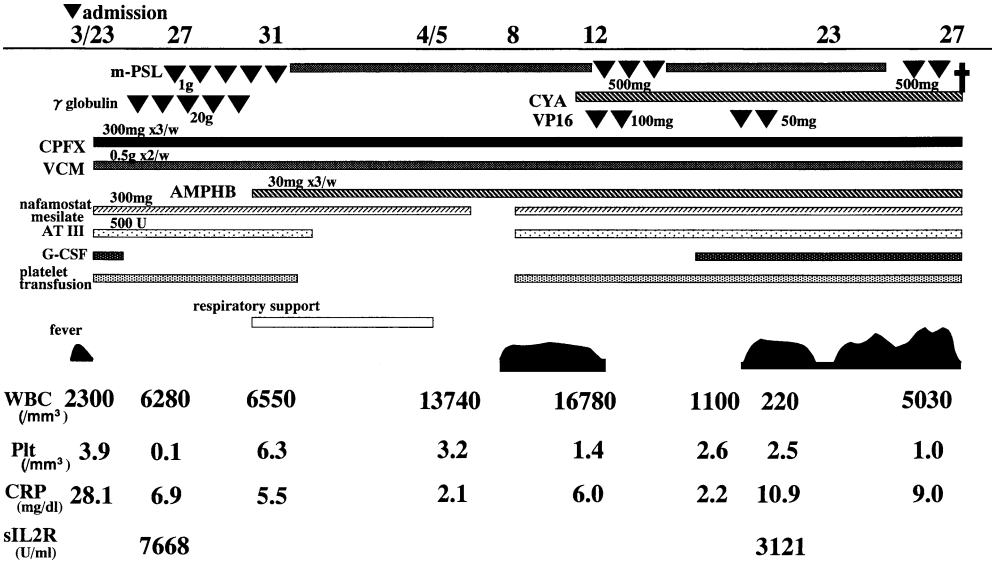

Fig. 3. Clinical course. *m-PSL*, methilprednisolone; *CYA*, cyclosporine A; *VP-16*, etoposide; *CPFX*, ciprofloxan; *VCM*, vancomycin; *AMPHB*, amphotericin B; *ATIII*, antithrombin III; *G-CSF*, granulocyte-colony stimulating factor; *WBC*, white blood cells; *Plt*, platelets; *CRP*, C-reactive protein; *sIL2R*, soluble interleukin-2 receptor

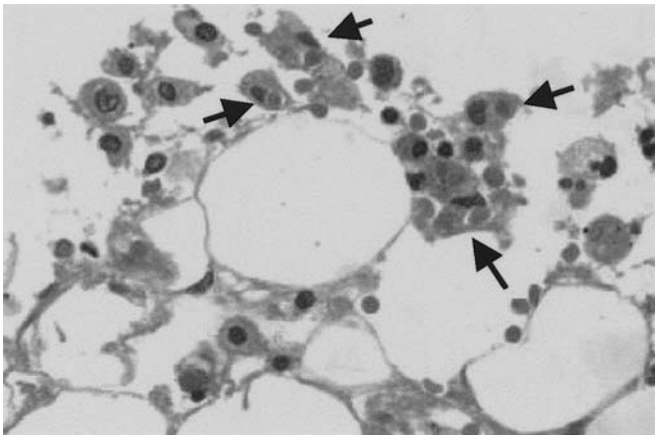

Fig. 4. Bone marrow. Hemophagocytic proliferation is evident in bone marrow (*arrow*). (H–E stain, ×150)

thought to result in clonal proliferation, resulting in the production of high levels of active cytokines.[1] Excessive production of inflammatory cytokines, such as IL-1, IL-6, soluble IL-2 receptor, TNF-α, and interferon-γ (INF-γ), promotes the activation of macrophages in this disease. The mechanisms of infection-associated HPS with nonviral agents are less well understood, but may also be related to high levels of active cytokines produced by host lymphocytes and monocytes, and may result from a poorly regulated or inappropriate cellular response to the pathogens.[1]

HPS is a rare disease with a high mortality rate, and the treatment of infection-associated HPS depends on its primary disease. Combined chemotherapy employing steroids, etoposide, and cyclosporine is recommended in virus-associated HPS, while bacteria-associated HPS may be resolved by treatment of the underlying infection.[1,3–6] The effect of intravenous immunoglobulin and antiviral chemotherapy in the treatment of HPS has also been reported. Plasma exchange to improve hypercytokinemia is reportedly worthwhile for HPS refractory to conventional chemotherapy.[7]

There have been two case reports of tuberculosis-associated HPS in patients undergoing hemodialysis.[3,4] One had a favorable clinical course after the administration of antituberculosis agents. In our patient, it is likely that *Peptostreptococcus*-induced sepsis and abscess formation in the left iliopsoas muscle were related to the onset of infection-associated hemophagocytosis. *Peptostreptococcus* is a gram-positive coccus which is widely distributed in the normal human flora, and it has been detected in systemic infections including those of the soft tissues. The bacteria was identified only once in the patient's blood culture when high fever and CRP elevation occurred, and we failed to confirm this agent in his left iliopsoas abscess at autopsy. As the abscess was found by CT scan soon after the fever occurred, it was thought that *Peptostreptococcus* might have caused the abscess formation. Hemophagocytosis persisted despite the antibiotic treatment, so we chose combined chemotherapy in this case. The disease course may also have been affected by the administration of drugs such as H_2 blockers, by autoantibodies against blood cells, and by *MRSA* infection after the onset of HPS. These complicating factors may lead to a poor response to antibiotics and chemotherapy.

Uremic patients on dialysis have an increased susceptibility to infections and risk of developing cancer.[8,9] Hemodialysis treatment leads to leukocyte activation and the overproduction of inflammatory cytokines. Increased plasma levels of cytokines, including IL-6, IL-8, and monocyte chemotactic peptide (MCP)-1, have been reported during hemodialysis treatment.[10–12] On the other hand, the peripheral blood mononuclear cells (PBMCs) of hemodialysis patients are reported to have impaired or paradoxical responses in cytokine production.[13,14] These findings are thought to be induced by blood–dialyzer interactions in hemodialysis, which play an important role in cytokine production and in the development of immunological abnormalities in hemodialysis patients.[15] Abnormal cytokine release and altered immunological responses by PBMCs in patients undergoing hemodialysis might have affected the

severe infection and the onset of hemophagocytosis in this patient. Further study will be needed to reveal the relationship between impaired cytokine release and its effects on cell-mediated immune responses in hemodialysis.

In conclusion, we report a case of infection-associated HPS in a patient receiving chronic hemodialysis. It is likely that the underlying diseases, including diabetes mellitus and ESRD, were related to the onset of hemophagocytosis.

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