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## A Case of Severe Sepsis Presenting Marked Decrease of Neutrophils and Interesting Findings on Dynamic CT

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Statistical Analysis C  
Data Interpretation D  
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**Conflict of interest:** None declared

**Patient:** Male, 60  
**Final Diagnosis:** Sepsis  
**Symptoms:** Fever • shock  
**Medication:** Sivelestat sodium hydrate  
**Clinical Procedure:** PMX-DHP • CHDF  
**Specialty:** Infectious Diseases

**Objective:** Unusual clinical course

**Background:** In a patient with severe sepsis, we sometimes observe immediate decrease of the counts of white blood cells (WBCs) and neutrophils, which is known as an indicator for poor prognosis. We observed marked decrease of white blood cells and neutrophils on blood examination and interesting findings on dynamic CT. Here, we present the case of a patient with severe postoperative sepsis occurring after major abdominal surgery and we discuss the mechanism of such clinical presentations.

**Case report:** A 60-year-old man received pancreatoduodenectomy with colectomy for pancreatic cancer. He developed a high fever on postoperative day 3. We observed marked decrease of WBCs and neutrophils on blood examination. We also observed slight swelling of the liver, inhomogeneous enhancement of liver parenchyma in arterial phase, and periportal low density in the Glisson capsule in portal phase, without any findings indicating infectious complications on dynamic CT. WBCs and neutrophils increased above normal range in just 6 hours. Blood culture examination performed while the patient had a high fever was positive for *Aeromonas hydrophila*. After receiving intensive care, he promptly recovered from severe sepsis. The CT findings disappeared on second dynamic CT examination performed 3 days after the first examination.

**Conclusions:** We treated a patient with severe sepsis after major abdominal surgery who presented very rapid change of the counts of WBCs and neutrophils and interesting CT findings in the liver. We rescued him from a critical situation by prompt and intensive treatment. Research is needed to accumulate and analyze data from more patients who present a similar clinical course to better understand their pathophysiological conditions.

**MeSH Keywords:** Multidetector Computed Tomography • Neutrophils • Sepsis

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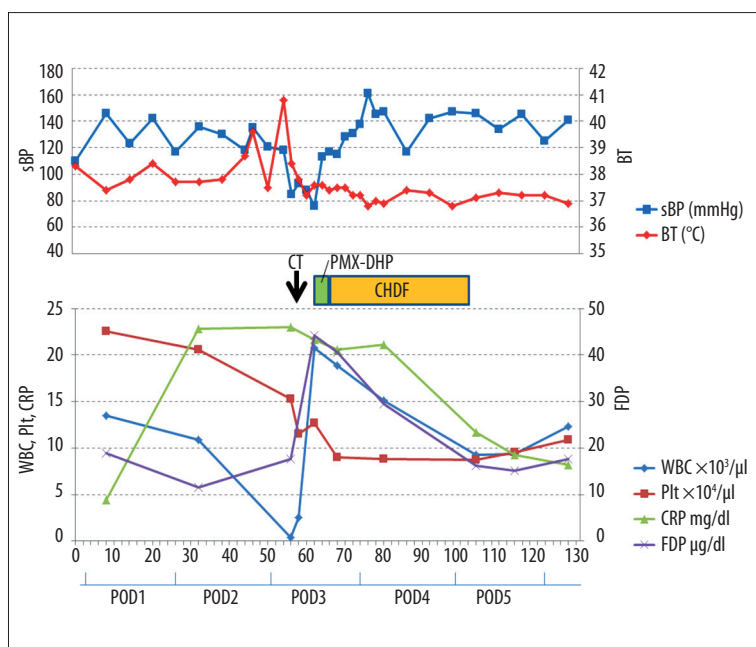
## Background

In a patient with severe sepsis, we sometimes observe immediate decrease of the counts of white blood cells (WBCs) and neutrophils[1], which is known as an indicator for poor prognosis [2]. We present the case of a patient with severe sepsis due to bacteremia with *Aeromonas hydrophila* that occurred after pancreatoduodenectomy for pancreatic cancer. We observed marked decrease in the counts of WBCs and neutrophils, followed by immediate increase a short time later. Simultaneously, interesting findings were obtained on dynamic CT. We discuss the immediate reaction of neutrophils against bacteremia and the mechanism of the CT findings obtained in this patient.

## Case Report

A 60-year-old man was admitted to our institute for surgical treatment for pancreatic cancer. Two years prior to the admission, he received total gastrectomy and splenectomy for advanced gastric cancer, followed by adjuvant chemotherapy with S-1 for a year. He had no significant medical history except for gastric cancer. There was no evidence of recurrence of gastric cancer on regular radiological checkup at every 3 months; however, a pancreatic tumor was detected about 2 years after surgery for gastric cancer. On dynamic CT, a poorly enhanced tumor, 18 mm in size, was detected in the head of the pancreas. It had invaded into the duodenum and transverse colon, and presented positive uptake on fluorine-18 fluorodeoxyglucose

positron emission tomography (FDG-PET). We diagnosed the tumor as a pancreatic cancer and performed pancreatoduodenectomy with extended right hemi-colectomy. Intraoperative blood loss was 800 ml and he received no blood transfusion. We resected the pancreatic cancer without any residual tumor on postoperative pathological examination. The postoperative course is summarized in Figure 1. About 54 hours after surgery, he suddenly developed high fever (up to 40.8°C) and shivering. The laboratory data at 2 hours after the high fever presented are shown in Table 1, showing remarkable decrease of the counts of WBCs to 420/ $\mu\text{L}$  and neutrophils to 310/ $\mu\text{L}$  and the count of platelets was 153 000/ $\mu\text{L}$ . They changed to 2570/ $\mu\text{L}$ , 2460/ $\mu\text{L}$ , and 115,000/ $\mu\text{L}$ , respectively, on reexamination at about 1.5 hours later. CT scan, which was performed about 5 hours after presentation of high fever, showed slight swelling of the liver. The liver parenchyma was inhomogeneously enhanced in arterial phase and almost homogeneously enhanced in portal phase on dynamic study. Periportal low density in the Glisson capsule was also observed in portal phase (Figure 2A, 2B). There were no abnormal fluid collections in the abdominal cavity or other findings indicating infectious complications. He presented shock just after the CT examination. Because hypotension persisted despite administration of doripenem and continuous infusion of dopamine, we started polymyxin B immobilized fiber column direct hemoperfusion (PMX-DHP) followed by continuous hemodiafiltration (CHDF) from 8 hours after presentation of high fever to reduce endotoxin and inflammatory cytokines. Simultaneously, we started continuous infusion of sivelestat sodium hydrate for the purpose of reducing excessive effect of neutrophil elastase.



**Figure 1.** Postoperative course. About 54 hours after surgery, he suddenly developed high fever (up to 40.8°C) with shivering. About 2 hours after high fever began, we observed a marked decrease of white blood cells followed by moderate decrease of platelets. Septic shock developed about 5 hours after the high fever began. White blood cells were rapidly increased without any intervention and he recovered from shock after beginning polymyxin B immobilized fiber column direct hemoperfusion followed by continuous hemodiafiltration. sBP, systolic blood pressure; BT, body temperature; PMX-DHP, polymyxin B immobilized fiber column direct hemoperfusion; CHDF, continuous hemodiafiltration; WBC, white blood cell; Plt, platelet; CRP, c-reactive protein; FDP, fibrin/fibrinogen degradation products; POD, postoperative day.

**Table 1.** Laboratory data at two hours after high fever-up.

(normal range)		(normal range)	
Hematology		Chemistry	
WBC	0.42×10 <sup>3</sup> /μL (3.3–8.8)	UN	17 mg/dL (8.0–22.0)
RBC	3.34×10 <sup>6</sup> /μL (4.3–5.5)	Creatinine	0.74 mg/dL (0.60–1.00)
Hb	9.8 g/dL (13.5–17.0)	Na	137 mEq/L (135–149)
Ht	28.6 % (39.7–51.0)	K	3.8 mEq/L (3.5–4.9)
Neutrophil	0.31×10 <sup>3</sup> /μL (1.58–6.34)	Cl	100 mEq/L (96–108)
Lymphocyte	0.11×10 <sup>3</sup> /μL (0.66–3.70)	ALP	183 IU/L (115–359)
Platelet	153×10 <sup>3</sup> /μL (130–350)	γ-GTP	15 IU/L (10–47)
CRP	23.0 mg/dL (<0.3)	AST	75 IU/L (13–33)
<b>Coagulation test</b>		ALT	64 IU/L (8–42)
PT	12.4 sec (10.5–12.9)	LDH	213 IU/L (119–229)
PT-INR	1.11 (0.83–1.04)	Amylase	95 IU/L (40–113)
APTT	27.4 sec (27.3–40.3)	Creatine kinase	1001 IU/L (62–287)
Fibrinogen	785 mg/dL (183–381)	Total bilirubin	1.0 mg/dL (0.3–1.2)
FDP	17.7 μg/mL (<5.0)	Total protein	5.2 g/dL (6.7–8.3)
FDP-DD	9.1 μg/mL (<1.0)	Albumin	2.6 g/dL (4.0–5.0)

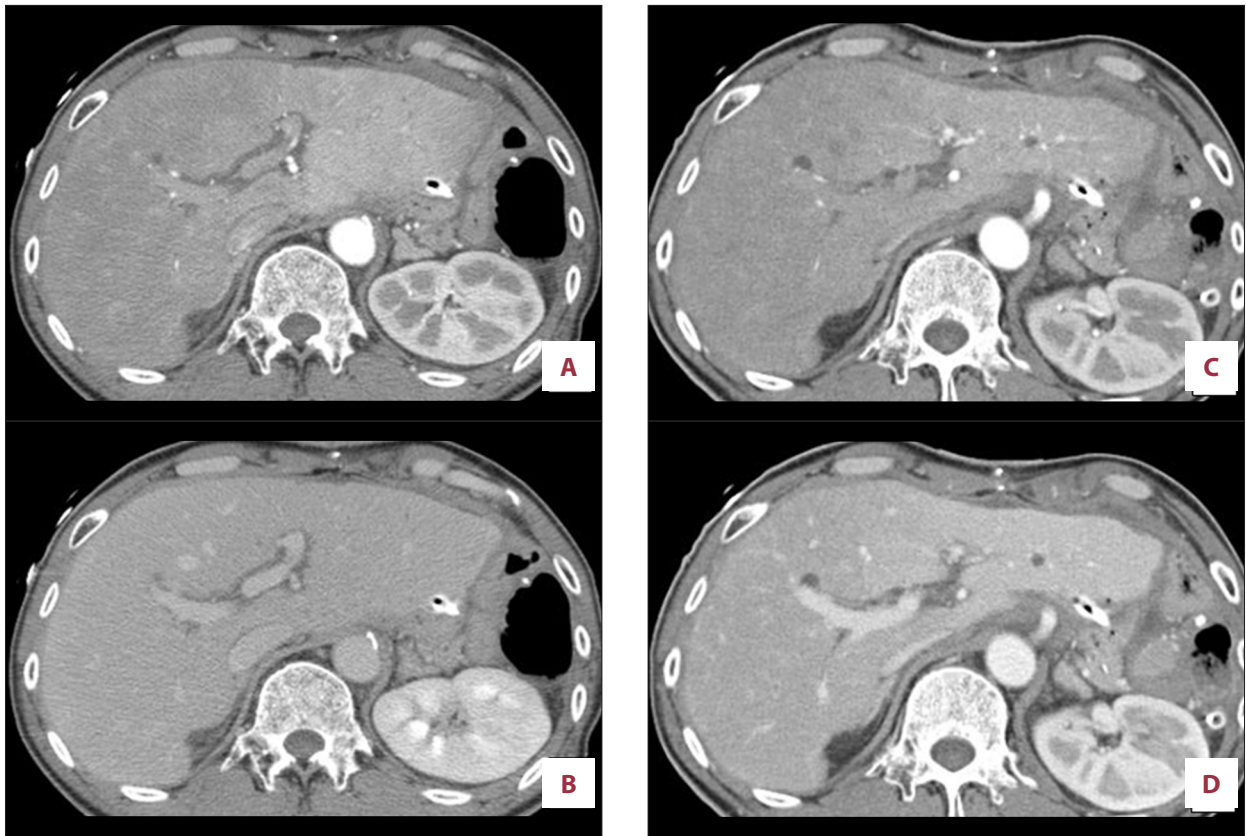
Just before starting PMX-DHP, WBCs, neutrophils and platelets changed to 20 730, 20 250, and 127,000/μL, respectively, without any intervention. The patient promptly recovered from septic shock after beginning of PMX-DHP followed by CHDF. The blood culture examination during high fever was positive for *Aeromonas hydrophila*. On the second CT scan, performed 3 days after the first examination, swelling of the liver and periportal low density in the Glisson capsule were improved, and inhomogeneous enhancement of the liver parenchyma in arterial phase became obscure (Figure 2C, 2D). After recovering from septic shock, his clinical course was uneventful except for incisional surgical site infection. He was discharged from our hospital 47 days after surgery.

## Discussion

Bacteremia with *Aeromonas hydrophila* is an uncommon infectious disease that usually occurs in immunocompromised patients with conditions such as liver cirrhosis, malignant disease, severe trauma, or burn injuries [3–6]. Bacteremia with *Aeromonas hydrophila* has a high fatality rate (30–70%) [7–10]. In this case of severe sepsis due to bacteremia with *Aeromonas hydrophila* that occurred after pancreatoduodenectomy associated with colectomy, we observed a very rapid change in the counts of WBCs and neutrophils. Although the counts of WBCs and neutrophils decreased to 420 and 310/μL, respectively, about 2 hours after presentation of high fever,

they increased to 20 730 and 20 250/μL, respectively, in just 6 hours, without any intervention. During these 6 hours, he began to present septic shock and significant findings were obtained by dynamic CT study.

The important findings obtained by dynamic CT in this case were slight swelling of the liver, inhomogeneous enhancement of the liver parenchyma in arterial phase, and periportal low density in the Glisson capsule in portal phase. These findings are sometimes obtained in patients with severe acute cholangitis and acute pyelonephritis[11–15]. Inhomogeneous enhancement of the liver parenchyma in arterial phase on dynamic CT is an important finding of acute cholangitis, and caused by the process of inflammation in portal tracts, followed by dilation of the peribiliary plexus and increased hepatic arterial blood flow[11]. Although inhomogeneous enhancement of the liver parenchyma in arterial phase on dynamic CT is a characteristic finding in patients with acute cholangitis, this finding can also be observed in patients without any abnormalities in hepatobiliary systems, such as acute pyelonephritis[15] and bacteremia, as in our patient. We assume the dynamic CT findings of slight swelling of the liver, inhomogeneous enhancement of the liver parenchyma in arterial phase, and periportal low density in the Glisson capsule in portal phase are common findings for patients with severe sepsis regardless of its etiology. We should consider other mechanisms that account for the dynamic CT findings observed in such patients.

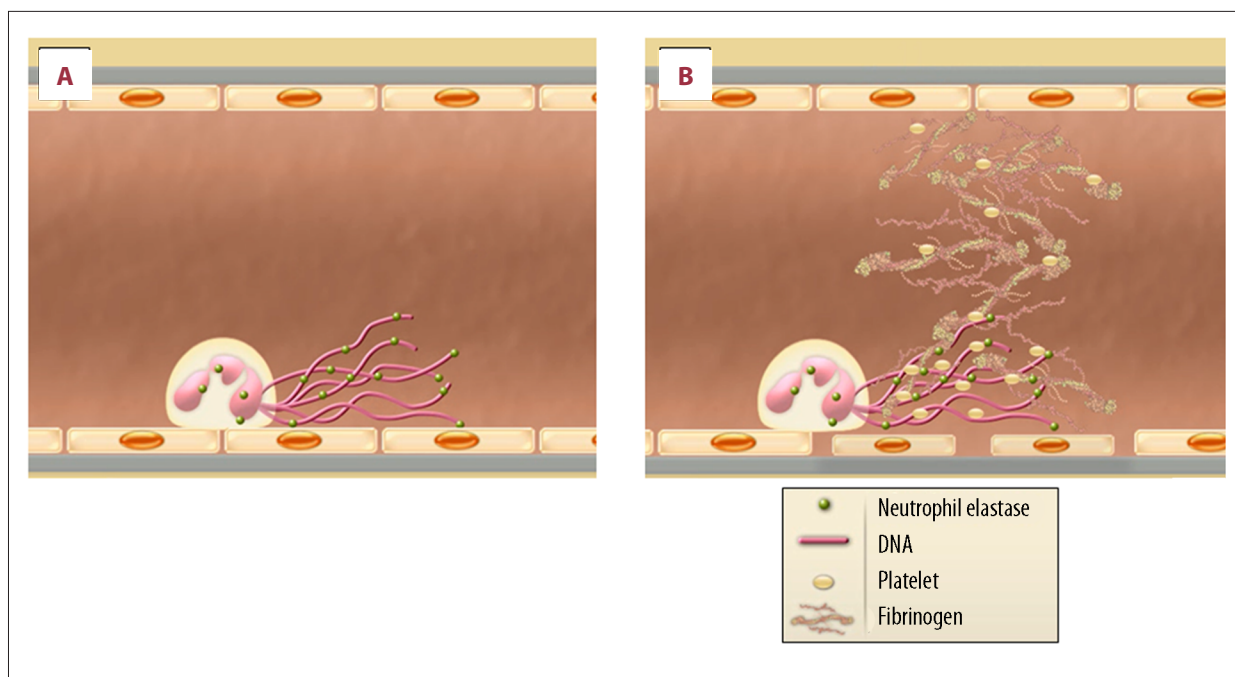


**Figure 2.** CT scan performed about 5 hours after high fever began (A, B), performed 3 days after the first examination (C, D). The liver had slightly swelling at first examination (A, B), and it was improved at the second examination (C, D). (A) The liver parenchyma was inhomogeneously enhanced in arterial phase on dynamic study. (B) Homogeneously enhanced and periportal low density in Glisson capsule was observed in portal phase on dynamic study. (C) Inhomogeneous enhancement of the liver parenchyma in arterial phase became obscure. (D) Periportal low density in Glisson capsule was also improved.

Recently, a new concept of “neutrophil extracellular traps” (NETs), which is a biophysical mechanism of neutrophils against bacteria, has been proposed [16–21]. Activated neutrophils release granule proteins, such as neutrophil elastase and myeloperoxidase, histones, and deoxyribonucleic acid (DNA), which together form extracellular fibers and bind bacteria (Figure 3A). These NETs degrade virulence factors and kill bacteria. This self-sacrificing mechanism of neutrophils against invading bacteria is called “NETosis”. Although NETs have the beneficial effect of trapping bacteria in infectious disease, excessive formation of NETs also causes unintended injury to the host [22–25]. NETs bind not only bacteria but also platelets to support their aggregation and provide a stimulus for their activation. NETs promote formation of microvascular thrombus through several pathways, such as activation of tissue factor pathway, platelets recruitment and activation, inactivation of anticoagulants including thrombomodulin and tissue factor pathway inhibitor (TFPI), and direct activation of factor XII (Figure 3B). These mechanisms are called immunothrombosis [26], and excessive microvascular thrombosis causes disorder of microcirculation and leads to organ dysfunctions.

Although the concept of NETosis is now used in molecular biology, the clinical stigma remains unclear. We presume that the clinical symptom of decreased counts of WBCs and neutrophils in patients with severe sepsis is caused by excessive NETosis. In response to inflammatory stimuli, neutrophils migrate from circulating blood to infected tissues and NETosis is induced. In the situation of severe bacteremia, many neutrophils are consumed for prompt elimination of bacteria through NETosis. In the present case, we observed very rapid change in counts of WBCs and neutrophils. Although we had no data supporting participation of NETosis, we assumed that immediate and dynamic reaction of neutrophils against bacteremia had occurred, and the findings on dynamic CT reflected some process of NETosis induced in the sinusoid of the liver. Although our patient had severe sepsis associated with shock and marked neutropenia, he recovered from the septic condition without any organ dysfunction. We believe that the induction of hemo-catharsis therapy and infusion of sivelestat sodium hydrate in the early phase of sepsis was effective in removing harmful materials such as histone and neutrophil elastase induced by NETosis.





**Figure 3.** Schema of NETosis. (A) Activated neutrophils release granule proteins, such as neutrophil elastase and myeloperoxidase, histones and deoxyribonucleic acid, which together form extracellular fibers, which are called neutrophil extracellular traps (NETs), which bind bacteria. (B) NETs bind platelets to support their aggregation and activation. NETs promote formation of microvascular thrombus through several pathways. These mechanisms are called immunothrombosis. DNA, deoxyribonucleic acid.

Because we currently do not completely understand the detailed mechanism causing these CT findings in the liver and because the cause of such a reaction occurring in the liver in patients with severe sepsis remains unclear, experimental studies with animal models might be necessary to investigate histopathological reaction involving participation of NETosis occurring in the liver in the situation of severe sepsis.

## Conclusions

We managed a case of severe sepsis caused by bacteremia with *Aeromonas hydrophila* that occurred after major abdominal surgery in a patient who presented very rapid change in counts of WBCs and neutrophils and interesting CT findings in the liver. We could rescue him from critical situation by prompt and intensive treatment. We should accumulate and analyze data from more patients who present similar clinical course to better understand their pathophysiological conditions.

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