Acute Reversible Myocardial Depression Associated with Sepsis

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Abstract

A 30-year-old man was admitted to our hospital for left lobar pneumonia with septic shock. Acute left-sided heart failure became evident as sepsis developed. Echocardiography revealed diffuse severe hypokinesis of the left ventricle (LV) and a pulmonary artery catheter showed Forrester subset II hemodynamics. Along with amelioration of sepsis and decrease of the serum concentrations of tumor necrosis factor- α and interleukin-6, LV hypokinesis improved. It is suggested that the patient's heart failure may have been due to functional depression of myocardial contractility resulting from a direct effect of the cytokines towards the cardiomyocytes, the so-called "septic myocardial depression". (Internal Medicine 42: 60–65, 2003)

Key words: sepsis, left ventricular failure, proinflammatory cytokines

Introduction

Sepsis is often accompanied by shock characterized by a high cardiac index and a low systemic vascular resistance (1, 2), the so-called "hyperdynamic shock". However, some patients with septic shock have the complication of congestive heart failure without any evidence of organic heart disease and they exhibit transient left ventricular systolic dysfunction that recovers along with amelioration of sepsis (3–5). This phenomenon is termed "septic myocardial depression (6)" or "acute septic cardiomyopathy (7)". We describe a patient who developed severe transient myocardial depression associated with sepsis caused by pneumonia.

Case Report

A 30-year-old man was admitted to our hospital on April 15, 2001, with high fever, left sided chest pain and dyspnea. His past medical history was significant for ulcerative colitis which had responded well to treatment with oral prednisolone and mesalazine. Several days prior to admission, he had a sore throat with a non-productive cough and was treated with oral antibiotics and non-steroidal anti-inflammatory agents.

On admission, he was fully conscious. His temperature was 38.7°C, with a blood pressure (BP) of 60/30 mmHg and pulse rate of 130/min. His skin was warm and moist but not cyanotic. No heart murmur, crackles or rubs were audible over his chest, but he had mild knocking pain on his left lateral chest. No abnormal findings were observed in the abdomen. Laboratory data showed elevated inflammatory reactions (white blood cell count (WBC), 10,400/mm³ (neutrophils, 71.5%); C-reactive protein (CRP), 5.8 mg/dl) and hypoxia. Other laboratory values included the following: hemoglobin, 15.0 g/dl; hematocrit, 44.6%; platelet, 23.0×10⁴/mm³; serum urea nitrogen, 14.1 mg/dl; serum creatinine, 1.1 mg/dl; sodium, 136 mEq/l; potassium, 3.1 mEq/l; aspartate aminotransferase, 30 IU/l; alanine aminotransferase, 27 IU/l; lactate dehydrogenase, 406 IU/l; amylase 58 IU/l; and total protein, 6.1 g/dl. Arterial blood gas while breathing room air showed the following: pH, 7.427; pO₂, 43.4 Torr; pCO₂, 36.3 Torr; HCO₃⁻, 23.9 mEq/l; base excess, 0.6 mEq/l; and O₂ saturation, 80.7%. Chest X-ray showed no apparent abnormal finding, but computed tomography revealed a consolidative shadow in the left lower lobe of the lung (Fig. 1, upper panels). Electrocardiogram (ECG) revealed sinus tachycardia.

The diagnosis of left lobar pneumonia with septic shock was made and then treatment with inhaled O₂ at 7 liter/min, intravenous fluid, steroid pulse therapy (methylprednisolone 1,000 mg/day) and antibiotics (meropenem 0.5 g/day and

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Day 1

Day 2

Day 4

Day 5

Figure 1. Chest X-ray and computed tomography on admission (upper panels) and chest X-rays during hospitalization (lower panels).

erythromycin 1,000 mg/day) was started. However, oxygenation was not sufficient and dyspnea and confusion developed. On the second hospital day, he was intubated and required mechanical ventilation and central venous catheterization. Central venous pressure was 9 cmH₂O. Dopamine and dobutamine were given and his BP rose to 90 mmHg. On the third hospital day, CRP elevated to 46.1 mg/dl and WBC severely decreased. Laboratory data showed multi-organ damage (Tables 1, 2). Endotoxin absorption and continuous venovenous hemodiafiltration (CHDF) were performed and clindamycin 1,200 mg/day and amphotericin B 30 mg/day were added. However, chest X-ray showed progressive deterioration with cardiomegaly and bilateral pleural effusion along with the appearance of consolidative shadow in the right lung. (Fig. 1, lower panels).

Echocardiography on the fifth hospital day revealed severe diffuse hypokinesis of left ventricle (LV) (Fig. 2, left panel), and Swan-Ganz catheter demonstrated a mean pulmonary artery wedge pressure of 25 mmHg and cardiac index of 3.0 l/min·m², Forrester subset II. Olprinone hydrochloride, PDE-III inhibitor, 0.15 µg/kg·min was started, and his hemodynamic status immediately improved to Forrester subset I (Fig. 3). Thereafter, the patient's condition gradually improved, but the causative organism for pneumonia and

sepsis was not identified despite extensive investigations for *Legionella pneumophila*, *Mycobacteria*, *Mycoplasma*, fungi, *Chlamydia*s, and viruses. Serum β-D-glucan before CHDF was elevated (165.9 pg/ml), suggesting that there might have been a fungal infection, but endotoxin was negative. On the seventh hospital day, when his hemodynamic status was in Forrester subset I, echocardiography still showed diffuse hypokinesis of LV. However, on the 32nd hospital day, when all the instrumentations, inotropic agents and antibiotics had been withdrawn, LV ejection fraction (LVEF) had improved to 63% and LV end-diastolic dimension had decreased to 46 mm (Fig. 2, middle and right panels). There was no significant ECG change during hospitalization and laboratory data did not reveal definite evidence of myocardial injury (Table 2). Radioisotope imaging showed normal myocardial perfusion and fatty acid metabolism. Cardiac catheterization performed on the 44th hospital day revealed no organic abnormalities of the heart; coronary arteriogram showed no significant epicardial coronary artery stenosis, left ventriculogram showed normal LV wall motion with LVEF of 78%, Swan-Ganz catheter demonstrated a mean pulmonary artery wedge pressure of 4 mmHg and cardiac index of 4.6 l/min·m², and myocardial biopsy of right ventricular septum revealed no evidence of myocardial

Table 1. Laboratory Data on Hospital Day 3

White blood cell count	1,800/mm ³	(3,500–8,000)
Neutrophils	46.2%	(30.0–80.0)
Lymphocytes	42.9%	(15.0–60.0)
Eosinophils	1.6%	(0.0–10.0)
Basophils	3.8%	(0.0–2.0)
Monocytes	5.5%	(1.0–10.0)
Red blood cell count	492×10 ⁴ /mm ³	(450–550)
Hemoglobin	15.4 g/dl	(14.0–16.0)
Hematocrit	43.7%	(40.0–50.0)
Platelet	21.4×10 ⁴ /mm ³	(15.0–40.0)
Total protein	5.3 g/dl	(6.5–8.3)
Albumin	2.4 g/dl	(3.5–4.8)
Aspartate aminotransferase	146 IU/l	(10–40)
Alanine aminotransferase	43 IU/l	(5–35)
Alkaline phosphatase	124 IU/l	(104–338)
γ-Glutamyltranspeptidase	38 IU/l	(0–70)
Amylase	54 IU/l	(40–160)
Blood urea nitrogen	33.5 mg/dl	(8.0–20.0)
Creatinine	3.1 mg/dl	(0.6–1.3)
Na	132 mEq/l	(135–147)
K	4.3 mEq/l	(3.6–4.8)
Cl	98 mEq/l	(98–108)
Creatine kinase	3,928 IU/l	(50–230)
MB isozyme of creatine kinase	8.5 ng/ml	(<7.5)
C-reactive protein	46.1 mg/dl	(0.0–0.4)

Table 2. More Laboratory Data on Hospital Day 3 (continued)

Arterial Blood Gas Analysis (Pressure support, FIO ₂ 80%)		
pH	7.394	(7.38–7.46)
pO ₂	104.2 Torr	(84–108)
pCO ₂	23.4 Torr	(32–46)
HCO ₃	14.3 mEq/l	(21–29)
Base excess	–7.9 mEq/l	(–2–2)
O ₂ saturation	97.9%	
Fasting Blood Glucose	153 mg/dl	(70–110)
Fibrinogen	650 mg/dl	(170–390)
Prothrombin time	18.0 seconds	(10.0–15.0)
Activated partial thromboplastin time	44.9 seconds	(24.0–34.0)
Fibrin/fibrinogen degradation products (FDP)	16.5 µg/ml	(0.0–10.0)
FDP-D dimer	8.4 ng/ml	(0.0–0.9)
Myosin light chain I	21.2 ng/ml	(<2.5)
Troponin T	0.01 ng/ml	(<0.10)
α-atrial natriuretic peptide	77.9 pg/ml	(<43.0)
B-type natriuretic peptide	1,364.4 pg/ml	(<18.4)

*Values within () show our institutional reference ranges.

Figure 2. Changes in echocardiographic findings (LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction).

Figure 3. Schematic presentation of the clinical course of this case (BP, blood pressure; CHDF, continuous hemodiafiltration; CI, cardiac index; CRP, C-reactive protein; IL-6, interleukin-6; LVESD, left ventricular end-systolic dimension; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; TNF-α, tumor necrosis factor-α; WBC, white blood cell count).

inflammation, abnormal substance deposition, or granuloma formation.

Serum concentrations of tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6) were markedly elevated (83 pg/ml and 3,040 pg/ml, respectively). And along with the amelioration of the patient's inflammation and cardiac function, both values of these cytokines fell beneath the reference level (Fig. 3). However, the serum concentration of IL-1 β was not elevated (less than 8 pg/ml) in either the acute or convalescent phase. The patient made a full recovery and was discharged without sequelae on the 56th hospital day.

Discussion

Septic shock is a common and serious disorder and its hemodynamics are characterized by a high cardiac index and a low systemic vascular resistance (1, 2), the so-called "hyperdynamic shock". However, it also has been reported that some patients with septic shock exhibit a transient depression of cardiac contractility and make rapid recovery along with amelioration of sepsis (3–5). This condition has been termed "septic myocardial depression (6)" or "acute septic cardiomyopathy (7)". Endotoxin (8, 9), TNF- α (9) and IL-1 β (10) have been reported to induce the same hemodynamic changes as seen in the clinical settings; hypotension and decrease in cardiac output, systemic vascular resistance and LVEF (8, 9). Experimental studies (6, 7, 10, 11) have shown that proinflammatory cytokines such as TNF- α (6, 7, 10, 11) and IL-1 β (6, 7, 10) induce a negative inotropic effect through nitric oxide (NO)-dependent (6, 10) or NO-independent (6, 7, 10, 11) mechanisms; TNF- α is reported to exert its myocardial depressant effects by activation of myocardial constitutive NO synthase (cNOS) and gene expression of inducible NOS (iNOS) leading to increased NO production. It also activates the sphingomyelin pathway leading to sphingosine production, which blocks the ryanodine receptor on the sarcoplasmic reticulum to impede Ca^{2+} -induced Ca^{2+} release (6, 10, 12). IL-6 production is activated by both TNF- α and IL-1 β and also has a negative inotropic effect through an NO-dependent pathway (11).

In the present case, the serum concentrations of some proinflammatory cytokines were markedly elevated when the patient had sepsis and acute left-sided heart failure, but there was no evidence of any cardiac disease or extracardiac conditions to induce acute left ventricular systolic dysfunction. Laboratory data suggesting myocardial injury such as elevated serum levels of troponin T were not obtained. Although the levels of creatine kinase, MB isozyme of creatine kinase and myosin light chain 1 (MLC1) were elevated, these biological markers are known to be elevated in patients with skeletal muscle injury. Radioimmunoassay system of MLC1 is known to partially cross-react with skeletal muscle MLC (13). There was no ECG change throughout entire period of hospitalization, even in the acute phase, also indicating that myocardial ischemia and/or injury were not present. Furthermore, cardiac catheterization confirmed that

there was no significant epicardial coronary artery stenosis and no evidence of organic myocardial injury suggesting myocarditis or specific cardiomyopathies in the biopsy specimen.

As mentioned earlier, endotoxin might have caused a transient LV systolic dysfunction (8, 9), but both endotoxin itself and endotoxin-producing bacteria were not detected from the sera of this patient. As a consequence, it was suggested that this patient's heart failure might have been due to functional depression of myocardial contractility resulting from a direct effect of the cytokines towards the cardiomyocytes, a pathophysiologic state compatible with the so-called "septic myocardial depression".

In contrast to the levels of TNF- α and IL-6, serum IL-1 β levels were not elevated in this case. TNF- α and IL-1 β have similar biological properties and often act synergistically (10), but clinical studies which have examined the serum levels of these proinflammatory cytokines during septic shock have constantly shown a lack of elevation of serum IL-1 β concentration despite a concomitant increased level of TNF- α (14, 15). These findings suggest that one cannot ascertain whether IL-1 β plays a role in the pathogenesis of septic myocardial depression in the clinical setting on the basis of serum IL-1 β concentration alone. On the other hand, the concentrations of the other cytokines TNF- α and IL-6 have been shown to be related to the severity of sepsis and prognosis of the patients with sepsis and/or septic shock (14, 15). This may reflect the pathophysiologic relation between these cytokines and "septic myocardial depression" previously shown in many experimental studies (6–10, 11).

In spite of these well-known experimental data, clinical case reports on this condition are few (5). The reason for this may be in part because these phenomena are not well recognized by many clinicians dedicated to critical care and efforts to further clarify the other etiologies of shock in such septic patients are not often made. However, as Parker et al reported (3), this condition is not rare in patients with sepsis. The present case suggests the importance to recognize that "septic myocardial depression" should be kept in mind when one sees septic patients with congestive heart failure, especially those with acute left-sided failure.

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