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Refractory gram-negative septic shock complicated by extended purpura fulminans and multiple organ failure in 23-year-old puerpera: A case report

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Notes

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T.Temirov (Data curation)
V.V.Kuzkov (Review and editing)

Informed consent

Signed informed consent for publication was taken and available for the editors.
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Refractory gram-negative septic shock complicated by extended *purpura fulminans* and multiple organ failure in 23-year-old puerpera

Running title: Refractory gram-negative septic shock
Abstract

**Background:** Pregnancy-related infections are the third most common cause of maternal death worldwide.

**Case:** A 23-year-old postpartum woman developed fulminate, refractory septic shock complicated by *purpura fulminans*, multiple organ failure syndrome (acute respiratory distress syndrome, acute kidney injury, encephalopathy). Patient’s management included antibacterial therapy, fluid and transfusion therapy, nutrition support, protective mechanical ventilation, hydrocortisone, a large dose of ascorbic acid and thiamine. There were no neurological consequences and all organ functions returned to normal parameters despite SOFA score-predicted hospital mortality was higher than 90%.

**Conclusions:** Septic shock is a significant and yet not completely understood life-threatening condition which can be associated with *purpura fulminans*, multiple organ dysfunction, disseminated intravascular coagulation and massive tissue necrosis.

**Keywords:** sepsis; septic shock; *purpura fulminans*; tissue necrosis; vasopressors; disseminated intravascular coagulation.
Pregnancy-related infection is the third most common cause of maternal death worldwide [1]. Sepsis represents one of the common cause of pregnancy-related mortality worldwide, while the most frequent being hypertension, abortion, and hemorrhagic complications [2]. The most common conditions and procedures leading to severe infection and sepsis in obstetrics include chorioamnionitis, septic thrombophlebitis, septic abortion, postpartum endometritis, puerperal sepsis, infection after cesarean section, episiotomy, wound infection, necrotizing fasciitis, pelvic abscess as well as hospital acquired infections such as ventilator-associated pneumonia, urinary tract infection, central line-associated infection [3]. The definition of refractory septic shock includes the following “the presence of hypotension with end-organ failure, requiring high-dose vasopressor support often greater than 0.5 μg/kg/min norepinephrine or equivalent” [4]. Despite recent advances, it is associated with mortality rate of 15–50%, furthermore, if vasopressor requirements for norepinephrine exceed 1.0 μg/kg/min, mortality rate can approach 80–90% [5]. The key component of refractory shock is severe tissue hypoperfusion, critical cellular and metabolic failure.

Lipopolysaccharide is a component of the outer membrane of gram-negative bacteria and is one of the key causative factors of septic shock in ICU patients [6]. The intravasation of gram-negative bacteria can trigger a cascade of systemic inflammatory reactions that frequently result in lethal outcome [7]. **Purpura fulminans** is a serious condition which usually occurs secondary to sepsis, can be associated with disseminated intravascular coagulation (DIC) and characterized by dermal vascular thrombosis and hemorrhagic infarction of the skin [8]. Sepsis-induced *purpura fulminans* involves a dysbalance of anticoagulant and procoagulant activities of endothelial cells. [9] This dysbalance is induced by endo- or exotoxintoxin in gram negative or gram positive sepsis respectively, mediated by cytokines resulting in the consumption of the proteins C and S and antithrombin III [9]. There are three main etiological subtypes of *purpura fulminans*: 1) idiopathic *purpura fulminans* – occurs in patients without
known or acute infections or the protein C pathway abnormalities; 2) acute infectious purpura fulminans – occurs in patients with acute severe mainly gram-negative bacterial infections; 3) occurs in patients with preexistent inherited or acquired abnormality of the protein C or protein S anticoagulant pathway [9]. In this case report, we presented a case of pregnancy-related infection who developed refractory septic shock accompanied by purpura fulminans and multiple organ failure.
Case Report

A 23-year-old postpartum woman with septic shock was transferred to the intensive care unit of the University Medical Center from rural regional hospital. During the pregnancy she was diagnosed with severe iron deficiency anemia (hemoglobin concentration 8.6 g/dL), gestational hypertension, meconium-stained amniotic fluid and prolonged rupture of membranes. There was no evidence of any evidence of infection over the period of pregnancy and no *Streptococcus* spp. was found in the vaginal smear. The course of pregnancy has been complicated by chorioamnionitis and urgent cesarean section performed several days before the transfer to our department. There was no any evidence of shock / end-organ dysfunction during labor. About 24 hours following cesarean section, the patient has developed clinical manifestation of purulent postpartum endometritis manifesting with fever of 39.0 °C, chills, purulent uterine discharge and fundal tenderness. She had an arterial line placed upon a diagnosis of endometritis. The blood cultures were taken before empiric antibacterial therapy was initiated (vancomycin and gentamicin). Several hours later she developed sepsis that abruptly transformed into septic shock (arterial pressure decreased to 60/40 mm Hg) and organ failure with 16–20 points on the sequential organ failure assessment (SOFA) score (10–12 points on the Glasgow Coma Scale, acute respiratory distress syndrome with PaO$_2$/FiO$_2$ 180 mm Hg, norepinephrine > 0.3 μg /kg/min (bodyweight 60 kg), bilirubin 23 mmol/l, platelets 35 × 10$^3$/μl, urine output 300 ml/day. Laboratory tests have shown multiple abnormalities including hemoglobin concentration of 7.7 g/dL, white blood cells 25×10$^9$/L, prothrombine time 21 sec, fibrinogen concentration 89 mg/dL, antithrombine III 53 %, D-Dimer 2.4 μg/mL (normal ranges in < 0.5), C-reactive protein 309.5 mg/L, procalcitonin 45 ng/ml, lactate 7.5 mmol/L, brain natriuretic peptide (BNP) 4000 ng/ml (Table 1). Protein C and protein S tests were not available due to technical limitations. A bolus of normal saline
(30 ml/kg) was given and immediate norepinephrine infusion (0.3 μg/kg/min) was initiated. Due to unstable condition the patient was intubated and respiratory support in assist-control mode was initiated. Within a short period of time, the dose of norepinephrine was increased up to 3.0 μg/kg/min to maintain the mean arterial pressure in a range of 60–65 mm Hg. Two hours after the onset of shock, the color of the fingers of upper and lower extremities as well as abdominal wall became mottled. Several hours later, echocardiogram demonstrated a left ventricle systolic dysfunction with an ejection fraction of 32% and dobutamine infusion (20 μg/kg/min) was started to improve cardiac contractility. The attempts to reduce the doses of catecholamines were unsuccessful due to insufficient hemodynamic response to fluid therapy. After the initial stabilization of the puerpera condition, hysterectomy was performed. Two days later, the patient was transferred to our hospital by sanitary aviation.

On physical examination upon admission to our department, we found massive aseptic necrosis of the all fingers (I–V), toes (I–V), metatarsal region and anterior abdominal wall (Figs. 1 and 2). The patient also has had sepsis/septic shock-induced failure of multiple systems including acute respiratory distress syndrome (ARDS), encephalopathy, systolic heart failure and acute kidney injury. An invasive blood pressure was 100/70 mm Hg, heart rate 150/min, arterial oxygen saturation 85–92% and body temperature of 38.4°C. The patient was sedated with dexmedetomidine (0.4 μg/kg/hr) and mechanically ventilated (assist/control ventilation with positive end expiratory pressure of 14 cm H₂O and FiO₂ 0.7). An auscultation has revealed crackles over the right middle and lower zones of lungs. Hemodynamic support has required intravenous norepinephrine 2 μg /kg/min and dobutamine 20 μg /kg/min.

The laboratory and instrumental findings that were taken in our department showed the following abnormalities: Hb 9 g/dL, WBC 22×10⁹/L, CRP 200.5 mg/L, lactate 4 mmol/L, procalcitonin 32 ng/ml,
creatinekinase MB 15.1 IU/L, BNP 5000 ng/mL, platelets $90 \times 10^9$/L, fibrinogen 114mg/dL, APTT 128 sec, INR 1.27, PT 16.9 sec (Table 1). Transthoracic echocardiography has demonstrated decreased (but improved compared to the previous values) ejection fraction of 38%. Chest radiography showed bilateral infiltrations (mild acute respiratory distress syndrome with $\text{PaO}_2/\text{FiO}_2$ 250 mm Hg). Blood culture showed multiple drug-resistant *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (all sensitive to meropenem). No microbial pathogens have been identified in the necrotic tissues. Patient management plan included antibacterial therapy, goal-directed fluid therapy, nutrition support, protective mechanical ventilation, hydrocortisone, fresh frozen plasma, a high dose of ascorbic acid and thiamine. The skin wounds were managed with dressing and moist healing products. Three weeks after admittance to our ICU the patient was weaned off the mechanical ventilation as well as from vasopressor therapy. There was no neurological consequences and all end-organ functions returned to normal parameters (even though, SOFA score-predicted hospital mortality was higher than 90%), but unfortunately necrotic area was quite massive. The duration of vasopressor support totaled 8 days. After stabilization of general condition the necrotic masses were debrided and autodermoplasty was performed.


Discussion

In our patient, refractory septic shock was complicated by purpura fulminans — a relatively infrequent symptom of DIC [10] which resulted in progressive tissue necrosis.

The presentation of such a massive lesion can be explained by a critical reduction of tissue perfusion due to purpura fulminance, probably heterogeneity of distribution of blood flow, endothelial injury, and impaired oxygen utilization. Success in septic shock management depends on early recognition and resuscitation. The effects of treatment can be improved and complications can be minimized by a balanced combination of fluid and vasopressor/inotropic therapy both should be initiated as soon as possible to improve microcirculation, blood fluidity, normalize coagulation to prevent severe ischemia-hypoxic tissue injury. Vasopressor therapy is one of the key components of septic shock management, especially if early fluid therapy cannot achieve the hemodynamic stabilization. However, high-dose vasoconstrictor therapy in hypovolemic patient might result in exacerbation of tissue ischemia and development of irreversible ischemic injuries such as digital necrosis as well as necrosis of internal organs. The advanced hemodynamic monitoring might be useful for personalizing fluid therapy and vasopressor/inotropic therapy.

This condition was complicated by a failure of cardiovascular, pulmonary, cerebral, renal, intestinal systems and massive necrosis of skin and subcutaneous tissue. Another interesting finding in our patient was that she developed sepsis-induced cardiac dysfunction just several of hours after the onset of sepsis. There was significantly elevated BNP of 5000 ng/ml and severe reduction of ejection fraction of 32 %, despite the fact that the patient had no history of cardiac problems. It has been shown that
cardiac dysfunction in septic shock patients was associated with a significant increase in mortality rate up to 70-90%, compared with 20% in those who did not have cardiac dysfunction [11].

The clinical manifestation of sepsis-induced *purpura fulminans* most commonly include purpuric rash as well as symptoms and signs of sepsis which usually preceded by fever or chills, sore throat, malaise. It has been shown that in about 67% *purpura fulminans* was associated with septic shock and in 78% with DIC [12]. The differential diagnoses include thrombotic thrombocytopenic purpura, postinfectious thrombocytopenic purpura, Henoch-Schonleinpurpura. [12] *Purpura fulminans* can be associated with the mortality rate approaching 50%. The standard management of *purpura fulminans* includes aggressive fluid resuscitation, inotropic therapy, respiratory support, coagulation control and management (fresh frozen plasma, anticoagulants), treatment of underlying infection, renal replacement therapy and management of complications. [13] Additionally, we suppose that our patient could benefit from early initiation of blood purification therapy with the use of cytosorbent or its analogues, however, we do not know whether it could prevent development of *purpura fulminance* and massive necroses, since the onset of septic shock was abrupt and it would take time for blood purification therapy to achieve its effect. In our opinion, early removal of endotoxin and inflammatory cytokines could probably attenuate multiple organ dysfunction and decrease the extent of organ failure.

In conclusion, septic shock is a significant and yet not completely understood life-threatening condition which can be associated with *purpura fulminans*, multiple organ dysfunction, disseminated intravascular coagulation and massive tissue necrosis.
References


Table 1. Clinical and Laboratory Characteristics of Multiple Organ Dysfunction in Our Patient

<table>
<thead>
<tr>
<th>Organ dysfunction</th>
<th>Patient’s parameters at time of septic shock onset</th>
<th>Patient’s parameters two days later</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Circulatory failure (reduced tissue perfusion); disorder of coagulation</td>
<td>Blood pressure 60/40 mmHg, Pulse rate 120 beats/min, Hyperlactatemia 7.5 mmol/L, Decreased capillary refill (Ischemia and necrosis of fingers, toes, skin of the abdominal wall), D-Dimer 2.4 µg/ml</td>
<td>Lactate 4 mmol/L, Creatine kinase- MB 15.1 IU/L, BNP 5000 ng/mL, Massive aseptic necrosis of the all fingers (I–V); toes (I–V), metatarsal region and anterior abdominal wall, D-Dimer 1.5 µg/ml</td>
</tr>
<tr>
<td>2 Myocardial dysfunction</td>
<td>Myocardial hypokinesis of anterior wall of LV, Reduced LV contractility, Ejection fraction 32%</td>
<td>Myocardial hypokinesis of anterior wall of LV, Ejection fraction 38%</td>
</tr>
<tr>
<td>3 Acute respiratory distress syndrome</td>
<td>PaO₂/FiO₂ 180 mmHg</td>
<td>PaO₂/FiO₂ 250 mmHg</td>
</tr>
<tr>
<td>3 Gastrointestinal tract</td>
<td>Paralytic ileus</td>
<td>Paralytic ileus</td>
</tr>
<tr>
<td>6 Systemic inflammatory response and infection</td>
<td>Procalcitvone test 45 ng/ml CRP 175,8 mg/L</td>
<td>Procalcitin 32 ng/ml Escherichia coli, Pseudomonas aeruginosa, and Acinetobacter baumannii were cultured in the blood</td>
</tr>
<tr>
<td>7 Cerebral dysfunction</td>
<td>Delirium,12 points on the GCS</td>
<td>Delirium, 13 points on the GCS</td>
</tr>
<tr>
<td>8 Renal dysfunction</td>
<td>Urine output 300 ml/day</td>
<td>Urine output 320 ml/day</td>
</tr>
</tbody>
</table>

LV: left ventricle, CRP: C-reactive protein, PaO₂: partial pressure of oxygen, FiO₂: fraction of inspired oxygen, BNP: brain natriuretic peptide, GCS: Glasgow Coma Scale.
Figure 1. Massive necrosis of the anterior abdominal wall.
Figure 2. Necrosis of the toes of the right foot.