J Anesth (2008) 22:173–176
DOI 10.1007/s00540-007-0599-6

Journal of
Anesthesia

Rhabdomyolysis induced by *Pseudomonas aeruginosa* sepsis

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Abstract
We describe advanced hemodynamic insufficiency and remarkably high myoglobinemia in a 77-year-old man who was admitted to the intensive care unit after total aortic arch replacement. Serum myoglobin showed an unusually high value (peak value, 155 030 ng·ml^{-1}). The patient died of sepsis and untreatable metabolic acidosis. *Pseudomonas aeruginosa* was detected in blood culture specimens after his death. On histopathological examination, dense congregations of gram-negative bacilli were present in clots in blood vessels, while congregations of gram-negative bacilli around the circumference of small blood vessels were particularly apparent in every specimen examined. Moreover, a generalized breakdown of muscle fibers, consistent with findings of rhabdomyolysis, was observed in muscle tissue throughout the body.

Key words *Pseudomonas aeruginosa* · Sepsis · Rhabdomyolysis

Introduction

While trauma, drugs, alcohol, coma, and infection are common causes of rhabdomyolysis [1], sepsis-induced rhabdomyolysis is relatively rare. In past reports, viral or gram-positive bacteria have been mainly implicated in rhabdomyolysis caused by infection [2], and rhabdomyolysis induced by gram-negative bacteria is very rarely encountered [3]. Here we report a case of rhabdomyolysis attributed to *Pseudomonas aeruginosa* sepsis, and confirmed later by pathological examination. In our understanding, this is the first case report of rhabdomyolysis associated with gram-negative infection to include histopathological findings.

Address correspondence to: Y. Fujino
Received: April 17, 2007 / Accepted: November 29, 2007

Case report

A 77-year-old man was transferred to the intensive care unit (ICU) after undergoing elective total aortic arch replacement with a four-branched graft to repair a thoracic aortic aneurysm. During the operation, due to hemodynamic instability, it was difficult to wean the patient from cardiopulmonary bypass (CPB), necessitating additional coronary artery bypass grafting (CABG) and continuous infusion of epinephrine 0.2 μg·kg^{-1}·min^{-1} and norepinephrine 0.15 μg·kg^{-1}·min^{-1}. Intraoperative blood loss was 2940 ml and the patient received large transfusions (autologous blood, 800 ml; red cells, 3900 ml; fresh frozen plasma, 2080 ml; platelets, 800 ml). Intractable bleeding, which may have been partially attributable to the prolonged CPB, resulted in an extended operation time of 13 h 30 min. After the operation, the patient was admitted to the ICU. On admission, blood gas analysis showed severe hypoxemia and metabolic acidosis: pH 7.142; base excess, BE, –12.1 mEq·l^{-1}; and Pa_{O_2}, 55 mmHg with fraction of inspired oxygen at 1.0. Subsequent to the initial surgery, the patient received two other operations on the same day, and one on the day after the first operation, to stop bleeding. A percutaneous cardiopulmonary support (PCPS) device was attached to treat persistent hypoxemia and circulatory insufficiency.

Continuous veno-venous hemofiltration (CVVHF) was started to remove excessive body water. In addition to the fluid replacement at a rate of 1800 ml·h^{-1} with CVVHF, continuous infusion of sodium bicarbonate was started, at 20 ml·h^{-1}, on post-operative day (POD) 3 to control metabolic acidosis. Cefazolin sodium was chosen as an antibiotic at first. Then it was switched empirically to vancomycin. On POD 1, we suspected hemolysis or rhabdomyolysis, from the reddish color change in the CVVHF waste fluid. After the ICU admission, serum myoglobin showed unusually high values, reaching 155 030 ng·ml^{-1} on POD 3 (Table 1). Whole-

Table 1. Laboratory findings

POD	1	2	3	4
CPK ($U \cdot l^{-1}$)	2963	5803	43778	89000
CPK-MB ($U \cdot l^{-1}$)	20	89	636	1405
MYO ($ng \cdot ml^{-1}$)	3659	19310	155030	132500
D-dimer ($\mu g \cdot ml^{-1}$)	<0.2	<0.2	<0.2	<0.2
Lactate ($mg \cdot dl^{-1}$)	82.9	79.3	83.5	216.6

POD, postoperative day; CPK, creatinine phosphokinase; MYO, myoglobin

body computed tomography (CT) revealed no evidence of necrotic tissue in the intestinal tract or elsewhere that would account for the metabolic acidosis. During the clinical course, the patient's skin became ischemic and necrotic. Untreatable metabolic acidosis caused death on POD 4. *Pseudomonas aeruginosa* was detected in blood cultures after death.

Histopathology

Skin exfoliation was observed over the entire body and this was attributed to small-blood vessel occlusion.

Histological findings

Congregations of gram-negative bacilli were observed surrounding small blood vessels in specimens from all parts of the body (Fig. 1). Large congregations of bacteria were also present in clots in blood vessels. Large congregations of gram–negative bacilli were also detected in muscles and, in almost all the samples taken from locations throughout the body, muscle-fiber denaturation, a definitive characteristic of rhabdomyolysis, was seen (Fig. 2).

Discussion

While severe rhabdomyolysis may be caused by infection, bacterial action rarely underlies the pathophysiology of extensive muscle breakdown. In the patient reported here, rhabdomyolysis developed after aortic arch surgery. This patient had a past history of abdominal surgery for left internal iliac aneurysm. Although there were no conclusive indications of intestinal perforation or ischemia due to occlusion of the mesenteric artery, we assumed that marked elevation of serum myoglobin and metabolic acidosis were consistent with generalized *Pseudomonas aeruginosa* infection originating in the intestine.

Infectious rhabdomyolysis is mainly attributed to viral, and to a lesser extent, bacterial causes [1]. In viral infection, direct muscle invasion has been proposed as the cause of tissue breakdown. By contrast, when rhabdomyolysis is associated with bacterial infection, in addition to direct bacterial invasion of muscle fibers, a number of other causative mechanisms have been suggested, including anoxia, impaired metabolism, hyperosmolality, inflammatory mediators, and toxins [3–5]. Gabow et al. [1]. have reported that sepsis accounts for 2% of cases of rhabdomyolysis. In another study, 4.3% of cases of severe rhabdomyolysis were attributed to "septicemia" [6]. In neither study were the causative microorganisms reported. Gram-positive bacteria are thought to pose the major risk, however, and gram-negative infections are relatively rarely associated with rhabdomyolysis [7].

Our patient showed mild hyperosmolality on POD 1 (336 $mOsm \cdot kgH_2O^{-1}$), which was treated with CVVHF. It remains unknown, however, whether hyperosmolality is a cause or a result of rhabdomyolysis. In a study by Betrosian et al. [2], creatinine phosphokinase values correlated well with plasma osmolality in patients with gram-positive sepsis, but no such correlation was found in the gram-negative subgroup. It is possible that different microorganisms produce rhabdomyolysis by different mechanisms. For example, certain microorganisms produce muscle injury by direct muscle invasion [8], while *Clostridium* and others produce myotoxins, and streptococcal and staphylococcal species produce pyrogenic toxin A [9]. In the patient reported here, the histological evidence may suggest that muscle ischemia due to disseminated intravascular coagulopathy (DIC) could have played a major role in the pathogenesis of the rhabdomyolysis. However, D-dimer stayed in the normal range during the patient's entire clinical course (Table 1), which was not suggestive of DIC. The highest endotoxin level during the clinical course was 6 $pg \cdot ml^{-1}$, a value slightly elevated above the normal range. The most probable explanation of the findings in our patient is that the toxins produced by massive *Pseudomonas aeruginosa* infection caused systemic tissue necrosis, resulting in severe metabolic acidosis.

We still do not understand why severe sepsis due to *Pseudomonas aeruginosa* developed in this patient. In immunocompromised hosts or patients with chronic liver disease [10,11], *Vibrio vulnificus* can produce rhabdomyolysis by causing necrotising vasculitis [12]. In our patient, there was no evidence of immunodeficiency or liver dysfunction. That was why we switched empirically to vancomycin from cefazolin sodium. It was after the death of the patient that we were able to determine that *pseudomonas* was detected in blood specimens.

In conclusion, we report a patient who died of rhabdomyolysis and multiple organ failure with severe metabolic acidosis arising from *Pseudomonas aeruginosa* infection. Rhabdomyolysis with gram-negative infection is rare, and this is the first such report to include histopathological findings.

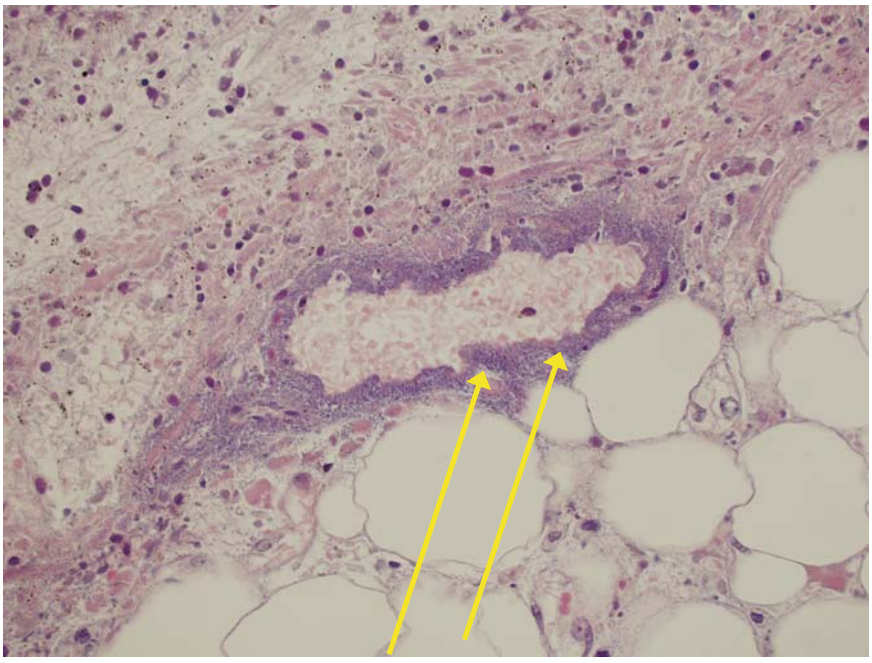

Fig. 1. Bacilli congregating around the circumference of a small blood vessel (*arrows*). Left heart ventricle. H&E, ×400

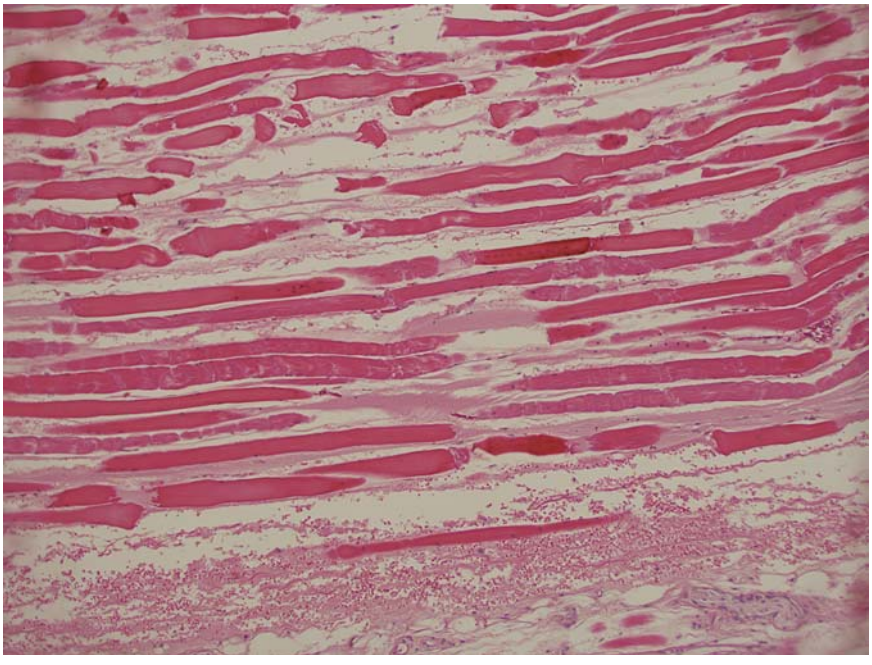

Fig. 2. Rhabdomyolysis in a specimen from inguinal muscle. H&E, ×400

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