Rhabdomyolysis Complicating Polymicrobial Sepsis in a Patient with Acute Leukemia

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Rhabdomyolysis with myoglobinuria is an uncommon complication of sepsis, whether monomicrobial or polymicrobial, even in its severe form. We describe a middle-aged woman with acute leukemia who developed rhabdomyolysis and myoglobinuria during the fatal course of chemotherapy-induced sepsis due to *Bacteroides thetaiotaomicron* and *Enterococcus faecalis*, followed by multiple organ dysfunction syndrome. In addition, autopsy revealed disseminated infections with *Aspergillus* and *Candida*. None of these organisms has been reported to be involved in the pathogenesis of rhabdomyolysis. Therefore, the etiology of the rhabdomyolysis in this case was probably multifactorial, with polymicrobial septic processes being possibly important contributing factors.

(Internal Medicine 35: 36–38, 1996)

Key words: myoglobinuria, neutropenic enterocolitis, disseminated mycosis, multiple organ dysfunction syndrome

Introduction

Rhabdomyolysis with myoglobinuria is well known to occur in association with acute toxic, metabolic, infectious, and traumatic muscle damage (1). However, this syndrome is uncommonly described in reviews of septic manifestations, even as a part of multiple organ dysfunction syndrome (MODS) induced by sepsis (2–5). We describe a patient with acute leukemia who developed rhabdomyolysis and myoglobinuria during the fatal course of severe bacterial and fungal sepsis associated with intensive chemotherapy. To our knowledge, such a case of polymicrobial sepsis-associated rhabdomyolysis has not been reported previously. The overall severity of the septic processes seemed to play a role in the pathogenesis of the rhabdomyolysis in our patient.

Case Report

A 42-year-old woman presented with a low-grade fever and nasal bleeding, and acute lymphocytic leukemia was diagnosed. She underwent antileukemic therapy including enocitabine administration, followed by treatment with granulocyte colony-stimulating factor. She was also empirically placed on broad-spectrum antibiotics. However, an abrupt

high fever up to 40.5°C occurred when her neutrophil count fell to 0/μl. She developed nausea, vomiting, abdominal pain, and diarrhea. Blood cultures grew no organisms. Antibiotic therapy was changed to ceftazidime and gentamicin in combination with fluconazole, but with no apparent effect. Two days later, she developed hypotension and intravascular coagulation (DIC), and adult respiratory distress syndrome (ARDS), with transient hypoxemia to a PaO₂ of 46.5 Torr. Furthermore, the use of high-dose methylprednisolone led to transient hyperglycemia (446 mg/dl) accompanied by hyponatremia (161 mEq/l). Such complications associated with suspected sepsis were managed with routine methods. Soon thereafter, however, she complained of severe abdominal pain, with physical findings including abdominal distension, decreased bowel sounds, and rebound tenderness localized particularly to the right lower quadrant. Abdominal roentgenogram revealed evidence of paralytic ileus with some ascites and thickening of the bowel wall, suggesting neutropenic enterocolitis (6). Ultrasound-guided paracentesis disclosed a cloudy, yellowish fluid. Cultures of both blood and ascites grew *Bacteroides thetaiotaomicron*, which was isolated three days later from the blood together with *Enterococcus faecalis*. Both of these organisms proved to be resistant to ceftazidime and gentamicin, and sensitive to imipenem. Antibiotic therapy was changed to the latter agent alone. Late that

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Received for publication May 22, 1995; Accepted for publication October 17, 1995

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night, however, the urine color appeared dark reddish brown. The urine gave a strongly positive test for blood, but contained only a few erythrocytes. Serum sarcoplasmic enzymes were markedly increased: aspartate aminotransferase, 265 IU/l; lactate dehydrogenase, 2,274 IU/l; aldolase, 49.7 IU/l; creatine phosphokinase (CPK), 30,880 IU/l, with 99.3% CPK-MM (skeletal muscle band) and 0.7% CPK-MB (myocardium band), although alanine transferase remained slightly above high normal (58 IU/l) because of the preexisting fatty liver due to obesity. Serum potassium was also elevated to 5.7 mEq/l, while serum sodium and creatinine remained almost normal. In addition, testing for serum myoglobin revealed an extremely elevated level of 150,000 ng/ml (normal value for females: <35 ng/ml). She showed severe prostration with generalized aching pain. The urine output began to decrease gradually. Coincidentally, jaundice supervened and rapidly deepened. She died of massive gastrointestinal hemorrhage, with no evidence of marrow recovery.

Autopsy revealed hypoplastic bone marrow with minimal leukemic cell infiltration. Multiple hemorrhagic ulcerations were seen in the intestine distal to the ileum, especially the cecum. Some of these ulcerations disclosed full-thickness necrosis of the bowel wall containing numerous *Aspergillus* hyphae and bacterial masses without an associated inflammatory cell response. The hyphae penetrated the bowel wall into the subserous adipose tissue, occasionally showing vascular invasion. The lungs had several miliary microabscesses due to the same fungus with areas of confluent hemorrhage. The liver, with severe fatty changes, had microabscesses due to *Candida*, which was also found in some rectal ulcerations. Marked degeneration of muscle fibers with frank necrosis, as reported by others (7, 8), was found in the psoas muscle (Fig. 1). Multiple thrombi existed in the capillary vessels of the glomeruli, suggesting DIC. In addition, myoglobin casts in renal tubules with

some epithelial degeneration were detected by an immunostaining technique. Incidentally, no evidence of herpes-group viral infections, as indicated by intranuclear inclusion bodies, was found.

Discussion

Rhabdomyolysis associated with bacterial infection has been reported to occur as a concomitant condition of bacteremia (1). The causative organisms implicated include *Herbicola lathyri*, *Escherichia coli*, *Salmonella typhi*, *Legionella pneumophila*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*, but with no predilection for any particular bacterial species or group (1, 9). However, rhabdomyolysis has never been described even in a large series in the literature dealing with more than 500 patients with bacteremia, either monomicrobial or polymicrobial (4, 5). In this respect, rhabdomyolysis may well be regarded as an unusual septic complication.

Acute myopathic disorders are well known to occur only occasionally with influenza A or herpes-group viral infections (7, 10). The present patient, however, had no clinical or post-mortem evidence of such viral infections. Except for corticosteroids, the patient had not recently received any potentially myopathic medications reported to date (11). Steroid myopathy is usually characterized by normal serum CPK activity (11). Moreover, marked serum CPK elevation in diabetic patients usually suggests coincidental illness (11). The present patient developed steroid-induced, transient hyperglycemia with hypernatremia, which has been regarded as one of the rhabdomyolysis-associated factors (1). Such metabolic disorders, however, had resolved by the time rhabdomyolysis occurred.

The pathogenetic mechanisms involved in rhabdomyolysis remain to be elucidated. The clinical course of the present patient was seriously complicated by polymicrobial septic processes from neutropenic enterocolitis (bacteremia due to *B. thetaiotaomicron* and *E. faecalis*, disseminated aspergillosis and candidiasis, septic shock, and MODS including DIC, ARDS, and jaundice). None of these organisms has been reported to be involved in the development of rhabdomyolysis (1, 9). Considering the rarity of rhabdomyolysis in bacterial and fungal sepsis, therefore, the overall severity of the septic processes may underlie the pathogenesis of infection-induced rhabdomyolysis, and the etiology of the rhabdomyolysis in the present patient may be multifactorial.

Sepsis is defined as the systemic response to infection, which is mediated by inflammatory cytokines such as tumor necrosis factor and interleukin-1 (IL-1) (12). Baracos et al (13) have recently shown that IL-1 can act on skeletal muscle to stimulate intralysosomal proteolysis by increasing the production of prostaglandin E₂, resulting in myalgia with fever. Therefore, the generalized aching pain in the present patient may have reflected systemic damage of the skeletal muscle. In addition, the preexisting severe fatty liver in this patient may have altered the hepatocellular and reticuloendothelial cell function, which

Figure 1. Psoas muscle showing markedly degenerated muscle fibers with frank necrosis, occasionally interspersed with normal-appearing muscle fibers, without associated inflammatory cell response (HE stain, ×200).

plays a major role in the development of MODS (14).

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