Varicella Zoster Infection, Massive Rhabdomyolysis, Myoglobinuria, And Renal Failure

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Rhabdomyolysis, myoglobinuria, and resultant renal failure are associated with a large number of disease processes and causes. We describe here a case of rhabdomyolysis and myoglobinuria with resultant renal failure that was associated with varicella zoster infection. We were unable to uncover any other reported cases associated specifically with varicella zoster infection.

Case Report

A 16-year-old African-American boy with a 1-week history of chickenpox came to our emergency department complaining of increasing weakness, nausea, vomiting, and poor oral intake. He had previously been in good health. He had two young siblings who had had chickenpox 2 weeks before the onset of his signs and symptoms. His siblings' infections resolved without complications. The patient's mother noted that he seemed much sicker than his younger siblings and had a decrease in his urine output for the past 24 hours. His medical history indicated the patient had been in good health all of his life with only minor illnesses. His family history was remarkable for hypertension and a seizure disorder in a maternal aunt. The patient lived with his mother and younger siblings. He smoked one-half to one pack of cigarettes per day. He denied the use of alcohol, illicit drugs, or over-the-counter medications.

On physical examination he was an ill-appearing adolescent in no acute distress. His oral temperature was 95.4°F, heart rate 90 beats per minute, respirations 24/min, and blood pressure 157/89 mmHg. His weight was 134 pounds, which represented a 6-pound weight loss from his base-line weight of 140 pounds. He was alert, oriented, and cooperative. Findings from the patient's head and neck examination were unremarkable. He had a regular heart rate and rhythm, with tachycardia. His lungs were clear, and his abdomen was soft and nontender. He had normal bowel sounds. His extremities showed no clubbing, cyanosis, or edema. His skin had a diffuse vesicular rash that involved scalp, head, face, torso, and extremities, but it did not involve the palms of his hands or the soles of his feet. The lesions were in "crops," with some partially healed and some lesions just beginning. There was no redness, swelling, or tenderness of muscles or joints.

The patient was admitted to the hospital with the diagnosis of varicella zoster infection and dehydration. An intravenous drip of normal saline was started, and patient's fluid level was replenished during the next 24 hours. He was also prescribed intravenous acyclovir.

On admission, we ordered blood cultures, an automated chemistry screening (SMA-7), complete blood count, and a urinalysis. Urinalysis showed proteinuria at greater than 300 mg/dL, with glucose positive at 250 mg/dL and ketones positive at 15 mg/dL. Urine was negative for bile, blood, and nitrite. Specific gravity was greater than 1.030. There were large numbers of white cells present and 2 to 4 red cells per high power field. A complete blood count showed a white cell count of 22,600/mm^3, with 70 percent segmented neutrophils, 15 percent band cells, 6 percent lymphocytes, and 9 percent monocytes. Hemoglobin was 14.7 g/dL, and hematocrit was 40.9 percent. Initial SMA-7 showed a sodium of 127 mEq/L, potassium 5.7 mEq/L, chloride 89 mEq/L, carbon dioxide 17 mEq/L, anion gap 26 mEq/L, glucose 152 mEq/L, and blood urea nitrogen (BUN) 59 mg/dL.

After approximately 24 hours of fluid hydration therapy, the patient improved but remained weak and had poor oral intake. His urine output was only 200 mL in the initial 24 hours after admission.

Results of repeat laboratory studies on the second hospital day showed sodium 127 mEq/L, potassium 5.8 mEq/L, chloride 93 mEq/L, carbon dioxide 18 mEq/L, anion gap 22 mEq/L, glucose 115 mEq/L, BUN 61 mg/dL, creatinine 5.1 mg/dL, with a BUN-creatinine ratio of 11.96. At that

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time a diagnosis of acute renal failure was made, a nephrologist was consulted, and the patient began dialysis for his acute renal failure. A repeat SMA-18 showed the patient's sodium had fallen to 122 mEq/L, potassium 5.9 mEq/L, chloride 88 mEq/L, carbon dioxide 18 mEq/L, anion gap 22 mEq/L, glucose 97 mEq/L, BUN 89 mg/dL, creatinine 7.9 mg/dL, calcium 4.6 mg/dL, phosphorus 10.5 mg/dL. Alkaline phosphatase was 83 mEq/L. Aspartate aminotransferase (AST) was 8,900 U/L. Lactose dehydrogenase was massively elevated at 309,120 U/L. Total bilirubin was 0.1 mg/dL. Total protein was 6.5 g/dL, albumin 3.9 g/dL, cholesterol 116 mg/dL, and uric acid 14.3 mg/dL. A urine myoglobin test was strongly positive. Total creatine phosphokinase was massively elevated at 1,977,600 U/L (normal range 55 to 170 U/L). The myocardial component of creatine kinase fraction was 73.1 percent.

Additional laboratory studies were done to rule out streptococcal infection: antistreptolysin-O titers, throat cultures, and blood cultures were all negative. Titers for influenza A and B were obtained, both acute and convalescent. The results were consistent with past immunity, but there was no evidence of recent infection. A renal sonogram showed kidneys of normal size and no evidence of obstruction or other abnormalities.

During the 3 weeks after beginning dialysis, the patient's renal function slowly returned to normal. He developed hypertension but responded well to nifedipine, and he was discharged from the hospital with essentially normal renal function.

Discussion

A useful clinical definition of rhabdomyolysis is skeletal muscle injury that alters the integrity of the cell membrane and allows the escape of cell contents into the extracellular fluid. One cell component is creatine kinase, which is a sensitive and readily available serum marker for rhabdomyolysis and can be measured by most routine laboratories.[1]

The usual causes of rhabdomyolysis, myoglobinuria, and acute renal failure are well documented in the medical literature. Common causes are alcoholism and drug abuse. Heroin and cocaine in particular can precipitate rhabdomyolysis. Influenza is the only viral disease associated with any consistency with rhabdomyolysis and myoglobinuria. Toxins and metabolic disorders can precipitate rhabdomyolysis[2] (Table 1); other potential causes include strenuous exercise, prolonged seizures, heat stroke, trauma, severe burns, prolonged coma, malignant hyperpyrexia syndrome, and myositis in general.

Physical examination in rhabdomyolysis is frequently unrevealing. Muscle pain and swelling, if present, can strongly suggest rhabdomyolysis. In several studies, however, 50 percent of patients with documented rhabdomyolysis had no complaints of muscle pain, and even fewer had evidence of muscle swelling. The accumulation of fluid in muscle tissue after intravenous hydration could be a clue to underlying rhabdomyolysis.[2]

Myoglobinuria is another marker of rhabdomyolysis, and its presence can confirm the diagnosis. Serum levels of myoglobin rapidly fall to normal, because it is cleared from the plasma within 1 to 6 hours of the insult.[4] Consequently, serum myoglobin levels are unreliable as a diagnostic tool, and the absence of myoglobin in the urine and in the serum does not eliminate the diagnosis of rhabdomyolysis. Creatine kinase, however, clears the serum more slowly as it has a half-life of approximately 1.5 days, which makes it more useful as a marker of rhabdomyolysis.[5]

Another supportive laboratory finding is a BUN to serum creatinine ratio of less than 10:1 because of the increased creatine in the serum, which is rapidly converted into creatinine. Potassium release from the muscle can also be reflected by hyperkalemia, particularly in the setting of volume contraction and renal impairment. Serum calcium can fall while the phosphate can be elevated, again as a result of muscle contents spilling into the serum and compromised renal function.

A laboratory caveat for the clinician is the presence of red-brown urine that tests strongly positive for blood by dipstick but no confirmation of red cells on microscopy. This finding should make the clinician suspect rhabdomyolysis and myoglobinuria. Hemoglobinuria, which can produce a similar result, can be differentiated from myoglobinuria by examination of the patient's serum. Pink-tinged serum suggests hemoglobin and hemolysis. Clear serum strongly suggests myoglobin. Several other substances can cause the urine to turn brown or red: hemoglobin, nitrofurantoin, metronidazole, sulfa compounds, chloroquine, methyldopa, levodopa, phenacetin, salicylates, methocarbamol, cresol, phenol, iron

Table 1. Causes of Rhabdomyolysis and Myoglobinuria.*

Primary Muscle Injury	***Decreased Energy Production (acquired)***	***Toxins***
Polymyositis	Potassium depletion (severe)	**Venoms**
Dermatomyositis	Phosphate depletion	Snake
Trauma or crush injury	Ethanol	Hornet
Severe burns	Myxedema	Brown recluse spider
Vasculitis	Hypothermia	**Drugs**
Increased Energy Consumption	Diabetic ketoacidosis	Cocaine
Strenuous exercise	***Decreased Muscle Oxygenation***	Heroin
Delirium tremens	McArdle disease	Ethanol
Status epilepticus	Sickle cell trait	Barbiturates
High-voltage shock	Decreased muscle blood flow (potassium depletion, compressive vascular occlusion, arterial thrombosis or embolism, prolonged cardiac surgery)	Propoxyphene
Tetanus	Carbon monoxide poisoning	Methadone
Hyperthermia	Shock	Codeine
Heatstroke and cramps	Trauma	Glutethimide
Amphetamine, phencyclidine (PCP, angel dust), or lysergic acid diethylamide (LSD) intoxication	***Infections***	Amphetamines
Succinylcholine administration	Tetanus	Licorice or carbenoxolone (severe potassium deficiency)
Muscular dystrophies	Leptospirosis	Amphotericin B
Decreased Energy Production (genetic or congenital)	Legionnaire disease	Diazepam
Diabetic ketoacidosis	Shigellosis	ε-Aminocaproic acid
Nonketotic hyperosmotic coma	Reye syndrome	Phencyclidine
Carnitine deficiency	Viral influenza	**Other**
Enzyme deficiency (musclephosphorylase, α-glucosidase, amylo-1,6-glucosidase, glucose-6-phosphate isomerase, phosphofructokinase, adenine deaminase, carnitine palmitoyl transferase)	Coxsackievirus infection	Isopropyl alcohol
	Myxoma virus infection	Ethylene glycol
	Infectious hepatitis	Hypernatremia
		Arsine
		2,4-Dichlorophenoxyacetic acid

*Adapted from Glasock. (3)

sorbitol citrate, porphyrins, *Serratia marcescens* infection, melanin (in melanoma), and homogentisic acid (in alkaptonuria).[6]

Several other viruses can cause some mild rhabdomyolysis, although massive rhabdomyolysis of this degree is distinctly unusual with viral diseases. Nevertheless, a virulent infection with a large inoculum could precipitate myoglobin-induced renal failure in the setting of volume depletion. The same degree of myoglobinuria in a well-hydrated patient would have little renal impact. Appropriate management of myoglobinuria includes correction of the precipitating event and aggressive fluid replenishment. Careful attention to electrolyte balance and recognition and treatment of coexisting renal failure are also important. Acyclovir might be useful in the treatment of varicella infections, but it must be started within 24 hours of the initial skin eruption to alter meaningfully the course of the illness.

Summary

We have presented a case of rhabdomyolysis and myoglobinuria with resultant acute renal failure in association with varicella zoster infection, an association not previously described. A patient who has a severe varicella infection and volume depletion might be at risk for this life-threatening complication. Early recognition and prevention, together with appropriate support, might prevent this potentially lethal condition.

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