Asymptomatic Rhabdomyolysis Of Unknown Etiology

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Abstract: A 7-year-old boy developed rhabdomyolysis with a peak creatine phosphokinase level of 261,400 IU/L after his appendectomy. These abnormalities occurred following a 2–3-day illness consisting of upper respiratory tract symptoms, fever, and abdominal pain mimicking acute appendicitis. At the time of operation, a normal appendix was removed, and mesenteric lymphadenitis was noted. The myoglobinuria and elevation of creatine phosphokinase were transient, and the patient remained asymptomatic. We review various causes of right lower quadrant pain and rhabdomyolysis and address the roles of malignant hyperthermia and infectious agents. The possible cause of the phenomena observed in this patient is discussed. (J Am Board Fam Pract 1990; 3:265-9.)

A 7-year-old white boy was brought in January 1988 to a small-town hospital in Nebraska because he had abdominal pain, anorexia, and vomiting for several hours preceded by myalgia, sore throat, and nonproductive cough of about 2-days' duration. His abdominal pain began in the epigastric area the afternoon of admission and by evening was predominately in the right lower quadrant. He denied diarrhea, constipation, or rectal bleeding.

The patient was born after a full-term pregnancy, and his vaginal birth was uncomplicated. He met all developmental milestones appropriately and had no history of major illness. He used no medications and had no allergies. The patient lived with his parents, an 8-year-old brother, and a 5-year-old sister in the town where the hospital is located. The family had no cats, but they did own a properly vaccinated dog.

Two cousins on opposite sides of the family were affected by cerebral palsy. One had trouble tolerating anesthetics, but this was not related to malignant hyperthermia. No family members were affected by malignant hyperthermia or any other musculoskeletal disease.

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On physical examination, the patient's temperature was 38.9°C (102.1°F); pulse, 120 beats per minute; respirations, 18 breaths per minute; and blood pressure, 110/70 mmHg. He appeared acutely ill. He had right-sided abdominal tenderness that was most pronounced at McBurney's point. He had palpable, mildly tender cervical, axillary, and inguinal lymph nodes.

His white cell count was 8.3×10^6/L (8300/μL) with normal values for the differential leukocyte count. Hemoglobin and electrolytes were normal.

Course of the Illness

A diagnosis of appendicitis was made, and the patient was taken to the operating room the same evening. He was given intravenous methahexital sodium (Brevital™) and succinylcholine and was intubated without difficulty. Anesthesia was maintained with nitrous oxide and fluothane. His body temperature was monitored throughout the procedure, and no elevation above baseline was noted. An appendectomy was performed through a right pararectus incision, splitting, not cutting, the abdominal wall musculature. The appendix appeared normal, an observation later confirmed by histological examination. The surgeon also noticed mesenteric lymphadenitis. The operation was completed in less than 1 hour; the patient was extubated and left the operating room in satisfactory condition.

On the first postoperative day, the patient described his urine as looking "like coke." Urinalysis showed 3+ to 4+ occult blood with 0–2 red cells per high power field. On day 2, the urine had returned to its normal color, and urinalysis

showed 1+ occult blood and 0–2 red cells per high power field. A urine sample taken on day 2 was sent to a referral laboratory, which was unable to determine whether it contained hemoglobin or myoglobin because of the small amount present in the sample.

On postoperative day 1, the patient's serum creatine phosphokinase (CPK) was 137,000 IU/L (normal value 0–190 IU/L). On day 2, serum was sent to a referral laboratory, where the CPK was 261,400 IU/L with 100 percent MM band present. On postoperative day 5, the CPK was 27,000 IU/L. Blood urea nitrogen and creatinine concentrations as well as urine output remained normal throughout hospitalization. On postoperative day 2, serum haptoglobin was 11.9 g/L (119 mg/dL), and a direct Coombs' test was negative.

On postoperative day 1, the white cell count was 16.2 × 10⁶/L (16,200/μL), but on day 3, the white cell count was 3.0 × 10⁶/L (3000/μL) with 40 percent segmented neutrophils, 2 percent band neutrophils, 56 percent lymphocytes, and 2 percent monocytes. On day 5, the white cell count was 2.7 × 10⁶/L (2700/μL) with normal values for the differential leukocyte count.

During his postoperative course, the patient had no complaints of muscular pain. He had a temperature of 100–101°F on postoperative days 1 through 3 and was afebrile thereafter. His physical examination did not show muscular tenderness or weakness. The patient was discharged on postoperative day 7.

On postoperative day 13, the patient's CPK was 453 IU/L. Although a repeat CPK level and a muscle biopsy might have been useful in establishing a diagnosis, the attending physician, after conferring with several consultants, elected not to pursue these tests. At the time of follow-up, the patient's parents were informed that malignant hyperthermia was a possible cause of the observed rhabdomyolysis. They were advised that future surgery on the patient or family members should be undertaken only when clearly necessary and with appropriate precautions at a medical center where anesthesiologists are experienced in the treatment of patients who might develop malignant hyperthermia.

Discussion

We have presented a 7-year-old boy who had a 2-day history of upper respiratory tract symptoms before undergoing an appendectomy because of right lower quadrant pain. His appendix was normal, and he had mesenteric lymphadenitis. Postoperatively, he developed transient myoglobinuria caused by rhabdomyolysis. His recovery was uneventful, and he has remained in good health.

In the following discussion, we consider possible causes of the right lower quadrant pain and rhabdomyolysis and whether a single cause can account for both conditions.

Fortunately, the task of determining the cause of right lower quadrant pain in this patient was simplified by the finding of mesenteric lymphadenitis during appendectomy and the absence of evidence of other disease processes (other than the rhabdomyolysis).

Mesenteric lymphadenitis refers to inflammation of lymph nodes in the area of the mesoappendix. It frequently occurs following a viral type of upper respiratory tract infection[1] and has been reported to occur in association with infections by adenoviruses,[1,2] parvovirus B₁₉,[3] influenza,[1] *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*,[4] and *Giardia lamblia*.[5] In addition, a number of organisms that produce a veratoxin thought to be responsible for hemolytic uremic syndrome have been reported to cause acute abdominal symptoms, usually in conjunction with diarrhea. These include *Salmonella*, *Campylobacter*, *Yersinia*, *Pneumococcus*, enterotoxic *Escherichia coli*, *Shigella*, and several viruses.[6] With the exceptions of *Yersinia*[4] and *Pneumococcus*,[1] these organisms have not been reported to occur in association with mesenteric lymphadenitis. Although all of the above are possible causes, influenza A infection seemed best for explaining the patient's prodromal symptoms of fever, myalgia, and cough, the presence of mesenteric lymphadenitis, and the predominance of lymphocytes in the white cell differential postoperatively. In addition, the condition occurred during the time of year when influenza infections are most common.

Analyzing the causes of rhabdomyolysis is a more difficult task. The largest reported series of patients with rhabdomyolysis is by Gabow, et al.,[7] who studied 77 patients during 87 episodes of rhabdomyolysis. In half of the cases with reliable histories, the patients did not complain of muscle pain. Swelling of the muscles was present in only 4 of 87 cases at the time of admission and became apparent after administration of intra-

venous fluids in 4 of 9 patients who were observed daily. Eleven patients had peak CPK levels greater than 20,000 IU/L with a range of 24,000 to 238,000 IU/L. Thirty-three percent developed acute renal failure. Eight patients died, although 4 had major trauma, burns, or gangrene that were major contributing factors.

Numerous causes of rhabdomyolysis were identified, including excessive muscle exertion, direct muscle trauma, ischemia, malignant hyperthermia, polymyositis, metabolic disorders, drug intoxication, toxic injury, and genetic disorders. No etiological factor could be identified in 3 percent of the cases. We considered several of these possibilities in attempting to explain our patient's case.

The first was the possibility of direct operative muscle trauma, although this seemed unlikely, because no muscle was incised. Several authors have reported postoperative increases in CPK,[8,9] but these elevations have been only in the range of 200 to 700 IU/L. The possibility of muscle damage from ischemia because of muscle compression intraoperatively was considered as well. We found 2 reports of this occurring. The first,[10] reported in 1953, described myoglobinuria and renal failure in a 35-year-old, obese man who was in an extreme knee-chest position during a 3-hour orthopedic procedure. In the second,[11] following a 6-hour procedure in the same position, the patient developed myoglobinuria, the peak CPK level was 4555 IU/L. Both patients complained of lower extremity pain postoperatively. It is difficult to imagine that our 7-year-old patient could have developed this sort of damage after just 40 minutes in a supine position, particularly because he had no postoperative pain other than that from his appendectomy incision.

A number of drugs have been reported to cause rhabdomyolysis in one of three ways. Intoxication from use of illegal drugs or alcohol can produce unconsciousness and prolonged ischemia in a limb that has been compressed for a number of hours.[12,13] Drugs have also been reported to produce rhabdomyolysis by causing excessive muscle contraction following overdose[14-16] and hypersensitivity reactions.[17] In 2 reports,[15,17] CPK levels exceeded 200,000 IU/L. Succinylcholine has also been reported to cause modest elevations in CPK levels, presumably because of muscle fasciculations.[18] Our patient had no signs of drug toxicity or hypersensitivity.

Because our patient developed rhabdomyolysis after receiving succinylcholine and inhalation anesthetics, we were concerned about the possibility of malignant hyperthermia (MH). This disorder is usually inherited in an autosomal dominant manner, although a less common variant, associated with multiple congenital abnormalities and known as the King syndrome, is inherited as an autosomal recessive trait.[19,20] The pathophysiology of MH is not well understood, but it seems to involve excessive release of calcium into the sarcoplasmic reticulum following administration of succinylcholine and inhalation anesthetics.[21] Subsequently, the patient develops prolonged contraction of skeletal muscle, hyperthermia, acidosis, marked muscle swelling, and increased levels of serum potassium, sodium, ionized calcium, CPK, and myoglobin. Body temperature may increase as rapidly as 1°C every 5 minutes. The episode is usually fatal unless promptly recognized and appropriately treated.

Several cases of a similar syndrome involving muscle destruction and variable degrees of contraction in the absence of hyperthermia following use of inhalation anesthetics have been reported.[22-25] In two of these reports,[22,23] patients were difficult or impossible to intubate, had obvious rigidity, and had severe muscle pain and weakness postoperatively. One patient died.[23] In two other reports,[24,25] the signs were less obvious, but both patients had no fasciculations after succinylcholine was given and were difficult to intubate. One patient[25] suffered a cardiac arrest postoperatively but was successfully resuscitated.

It is unlikely but not impossible that our patient had an episode of MH. He obviously did not have a classic case, because he had no hyperthermia (beyond his elevated preoperative temperature), rigidity, postoperative muscle pain, or evidence of metabolic abnormalities associated with MH. Even in the cases where there was evidence of rhabdomyolysis without hyperthermia or rigidity, the patients, unlike the one we report, showed abnormal reactions to succinylcholine and were difficult to intubate. Nevertheless, we still cannot be absolutely sure that this does not represent a rare variant of anesthetic- or succinylcholine-induced myopathy. A muscle biopsy and repeated CPK levels might have been helpful in establishing such a diagnosis, but these tests were not obtained.

Viral infection was another possible cause of rhabdomyolysis in our patient, because he had symptoms of an upper respiratory tract infection and cervical, axillary, inguinal, and mesenteric lymphadenopathy. In addition, the patient's decreasing white cell count with a lymphocyte predominance was consistent with a viral infection. Unfortunately, no viral antibody titers or viral cultures were obtained. However, the condition occurred during a season when influenza A infections were most prevalent in Nebraska[26] and Iowa.[27]

We reviewed the literature on rhabdomyolysis associated primarily with viruses and found 18 published reports of 36 cases. The most commonly implicated virus was influenza,[28-37] which accounted for 26 cases. Epstein-Barr virus was associated with 4 cases,[38-41] and herpes simplex type 2 was associated with 1 case.[38] Adenovirus,[42] echovirus,[43] *Shigella*,[44] aspergillosis,[45] *Staphylococcus epidermidis*,[45] and *Legionella pneumophilia*[45] have all been reported in association with rhabdomyolysis. Finally, the various organisms that produce veratoxin can cause rhabdomyolysis with or without hemolytic uremic syndrome.[6,20] These include *Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Pneumococcus*, and enterotoxic *Escherichia coli*. Patient ages were from 3[31] to 74[29] years. Peak CPK values were between 100 IU/L[34] and 200,000 IU/L.[31] A number of authors reported peak CPK values greater than 40,000 IU/L.[31,34,38,40,42,43,45] The mechanism of injury is unknown.

The temporal relation between the mesenteric lymphadenitis and rhabdomyolysis that occurred in our patient suggests the possibility of a common cause. The veratoxin-producing organisms mentioned above provide a plausible explanation because they have been associated with acute abdominal pain and rhabdomyolysis.[6] However, they are more commonly associated with hemolytic uremic syndrome and diarrhea, neither of which was present in our patient. We believe that an influenza A infection provided a particularly satisfactory explanation because it was prevalent at the time of this patient's illness, can cause rhabdomyolysis, and can probably cause mesenteric lymphadenitis. As interesting as these possibilities are, however, they remain speculative.

Summary

We have presented a case of mesenteric lymphadenitis mimicking acute appendicitis and treated by appendectomy. Postoperatively, the patient developed rhabdomyolysis with a dramatic elevation in serum CPK concentration. The exact cause eluded us, but a viral etiology was likely, namely, influenza A. Because rhabdomyolysis is a rare complication of influenza infections, we initially overlooked the need to obtain viral cultures and acute antibody titers. We considered the need for a muscle biopsy and further CPK levels to evaluate for MH but were unable to obtain these. In the absence of these data, this patient will be considered as though he is susceptible to MH in the event that further surgery is necessary.

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