Acute Severe Rhabdomyolysis in an Human Immunodeficiency Virus-Seropositive Patient Associated with Rising Anti-Coxsackie B Viral Titers*

ANNE BERESSI, B.S., ROBERT L. SUNHEIMER, M.S., STEVEN HUISH, B.S., CHRISTINE FINCK, B.S. and MATTHEW R. PINCUS, M.D., Ph.D.

Department of Pathology, SUNY Health Science Center, Syracuse, NY 13210

ABSTRACT

Very recently there have been sporadic reports of polymyositis in patients who are positive for human immunodeficiency virus (HIV). The cause of this condition has not been documented. Recent evidence has been presented which indicates that the Coxsackie B virus may be a causative factor. Presentation is made of a patient, a drug abuser who was found to be HIV-positive with severe polymyositis manifested by generalized muscle weakness and a total serum creatine kinase that reached the unusually high level of >600,000 U/L. This patient was found to have a rise in titer of Coxsackie B-4 virus antibodies. He was negative for a variety of possible infectious causes of this condition and was negative for both anti-nuclear antibodies (ANA) and rheumatoid factor (RF). It is concluded that a polymyositis may indeed be associated with immunosuppressed states and that Coxsackie B-4 virus may be an important causative factor.

Introduction

Polymyositis is an inflammatory myopathy characterized by symmetric muscle weakness, proximal more than distal. This condition results in elevated serum levels of creatine kinase (CK). Recently, it has been suggested that polymyositis may occur in association with human immunodeficiency virus (HIV) seropositivity, the etiology of which is currently controversial. Report is made of a patient, diagnosed as HIV-positive, who presented with values of CK of greater than 600,000 U/L and who exhibited rising titers to Coxsackie B-4 virus.

Case Report

The patient is a 30-year-old male with a history of intravenous drug abuse and an 18-month history of HIV seropositivity. He presented in the emergency room in acute renal failure. Prior to admission, he complained of generalized weakness, anorexia, and watery diarrhea of 3 to 4 days duration, with occasional chills and diaphoresis. Two days prior to admission, he began to experience myalgia of increasing intensity, particularly in the neck, abdomen, and both legs. The patient had no known...
family history of renal or musculoskeletal disease. He denied recent drug abuse, trauma, or vigorous exercise.

On physical examination the patient was found to be hypotensive with a blood pressure of 82 mmHg/palp. (Doppler), hypothermic (35.1°C), with a pulse of 90 beats per minute and a respiratory rate of 20. Results of a cranial nerve examination were normal. Extremities were cool and mottled in appearance; radial pulses were 1+ bilaterally; femoral and pedal pulses were not palpable. Motor exam showed marked weakness with 0 to 1/5 Medical Research Council (MRC) in the lower extremities and 3/5 in the upper extremities. Tendon reflexes were absent in the lower extremities and diminished in the upper extremities.

Laboratory results are as follows: serum CK was 600,900 U/L (normal 50 to 180), lactate dehydrogenase (LD) was 26,040 U/L (normal 94 to 200), aspartate amino transferase (AST) was 4,630 U/L (normal 8 to 39), and alanine amino transferase (ALT) was 716 U/L (normal 0 to 54). Urea nitrogen was 960 mg/L, and creatinine was 54 mg/L. Sodium was 124 mM/L, potassium was 8.0 mM/L, chloride was 94 mM/L, bicarbonate was 12 mM/L, with an anion gap of 19. The patient was anemic (hematocrit 25.9%, normal red cell indices). The prothrombin time and partial thromboplastin time were within normal limits, but the thrombin time was elevated to 30.8 sec (normal 16.5 to 24.5). Arterial blood pH was 7.26, with a pCO2 of 29 mmHg, a pO2 of 50 mmHg, and an oxygen saturation of 78 percent on four liters of oxygen by nasal cannula. The patient was notably dehydrated on admission, and originally the hematology profile was remarkable for a platelet count of 8.3 x 10^3/μL and a white blood cell count (WBC) of 12.2 x 10^3/μL.

The patient was placed on fluid replacement with normal saline, for 31 hours. A urine specimen obtained by catheterization appeared brown and cloudy with a specific gravity of 1.019, pH of 5.5, protein, 300 mg/dL, ketone, 5 mg/dL, trace of glucose and markedly elevated myoglobin. Urine red blood cells, bacteria, casts and crystals were not seen, and cultures were negative. Toxicology screens were negative for drugs of abuse.

Immunological studies for cytomegalovirus, cryptococcus, Toxoplasma gondii, Influenza A & B, Coxsackie A, hepatitis B surface antigen (HBsAg), anti-hepatitis C (HCV), and venereal disease (VDRL) were negative. A two-fold rise in titer (1:64 to 1:128 [significant titer cutoff 1:8]) of Coxsackie B-4 antibody over a 12 day period was demonstrated, suggesting possible recent infection and perhaps accounting for the patient's prodromal enteric symptoms. Titers to Coxsackie viral types B-1, B-2, B-3, B-5 and B-6 were all consistently lower than 1:8. All assays for antibodies to Coxsackie viruses were performed by a serum neutralization method.* All reference ranges for significant anti-Coxsackie antibody titers have been established in these laboratories as >1:8. Stool cultures for acid fast bacilli and Clostridium difficile were negative. Blood cultures for bacteria and fungi were obtained on multiple occasions and were consistently negative.

The patient's myopathy was treated symptomatically with narcotic analgesics. The patient apparently went into remission and appeared to have completely recovered by the fourth hospital day. At that time, although his CK remained elevated at 345,200 U/L, he denied any muscular pain (analgesics had been discontinued on the second day of hospitalization) or tenderness, and neuromuscular strength was rated 5/5 (MRC) bilaterally in both the upper and lower extremities. The patient remained in renal failure, requiring dialysis three times per week until the 21st hospital day. His course was also complicated by several opportunistic infections, including a lobar pneumonia which considerably prolonged the patient's hospital stay. These infections appear to be the first manifestations of acquired immune deficiency syndrome (AIDS) or aids related complex (ARC) in this patient. Other related findings include an extremely diminished CD4-positive lymphocyte level (28 lymphocytes/μL of which 1% were CD4 positive); normal 38 to 54 percent), CD4/CD8 ratio of less than 0.1 (normal >0.99), and a lack of response to an anergy panel. Twenty-eight days after the patient's admission, he was discharged, apparently free of infection and with no detectable neuromuscular sequelae. He was subsequently lost to follow up.

Discussion
A variety of neuromuscular disorders have been documented in association with AIDS, i.e., peripheral neuropathies,4 amyotrophic lateral sclerosis,4 nemaline rod myopathy,3,7 and acute rhabdomyolysis with myoglobinuria.8,10 However, polymyositis with subacute proximal muscle weakness and mild-to-moderate elevations of serum CK has also been reported in association with AIDS.4 It has been reported that polymyositis can occur as the initial clinical manifestation of HIV in patients who subsequently develop ARC within weeks and typical AIDS within months,1 or it can occur after the clinical onset of AIDS.7 The presenting symptom of myopathy is muscle weakness, usually proximal in distribution. It is difficult to distinguish between generalized weakness owing to the systemic disorders associated with AIDS and primary neuromuscular diseases.

* Smithkline Bioscience Laboratories, West Point, PA 19486.
The patient presented in this case report is unusual in that this condition appears to have had a very acute onset, and the serum CK was markedly elevated to an unusually high level of 600,900 U/L. This increase was accompanied by an increasingly intense, diffuse myalgia and severe myoglobinuria. All of these signs and symptoms characterize an acute polymyositis. Because no electromyographic or muscle biopsy studies were performed, this diagnosis has not been established definitively. However, the findings reported here strongly suggest this diagnosis as the correct one. The myopathy was treated symptomatically with narcotic analgesics, and the patient's condition resolved symptomatically by the fourth hospital day, although his serum CK remained elevated at 345,200 U/L.

The etiology of polymyositis remains unknown, although it is suspected to be either autoimmune or viral. It has been documented that Coxsackie B virus can be isolated from the inflamed muscle of patients suffering from polymyositis and a Coxsackie B infection. Also, other viruses, such as togaviruses and influenza viruses, are known to have a specific affinity for muscle of various host animals. In this case report, the patient had serologic studies for cytomegalovirus, cryptococcus, Toxoplasma gondii, Influenza A and B, Coxsackie A, hepatitis B surface antigen (HBsAg), HCV, and VDRL; all were negative. However, the patient did have a significant and specific rise in titer of Coxsackie B-4 antibody, suggesting a recent infection. The myotropism of Coxsackie viruses and their postulated involvement in idiopathic inflammatory muscle disease may have contributed to this patient's polymyositis.

It should be noted that to establish a definitive diagnosis of acute Coxsackie B-4 infection, it is generally accepted that there should be a four-fold rise in antibody titer over a period of up to four weeks. Here, a two-fold rise was found over a period of less than two weeks. Further follow-up of antibody titers was not performed on this patient. Therefore, the diagnosis of acute Coxsackie B-4 viral infection in this patient is a tentative one.

It has also been postulated that retroviruses such as HIV and human T-lymphotropic virus (HTLV) may play causative roles in the development of polymyositis either by direct invasion of the muscle or by an immune-mediated mechanism. In one study, polymyositis was induced by similar AIDS type D retrovirus in monkeys, and the retrovirus was isolated from homogenates of the muscle biopsy. In another case report, HTLV-III retrovirus was isolated from inflammatory cells surrounding muscle fibers of two patients with polymyositis who both subsequently developed AIDS. Possibly, therefore, HIV may have directly contributed to the polymyositis. Thus, in this case report, the patient's myopathy might have been directly caused by his infection with the AIDS retrovirus. However, since there have been no documented reports of HIV isolated from human muscle biopsies, it seems more likely that this condition was associated with Coxsackie B-4 viral infection.

References
5. Illa, I., Nath, A., and Dalakas, M. Immunocyto-


