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Rhabdomyolysis in Leptospirosis (Weil's Disease)

COLLEAGUES – Leptospiral disease may vary greatly in its nature and in the severity of its clinical manifestations. In severe cases, mortality reaches to 40%–50%, and myalgia and muscle injury are frequently observed but poorly understood [1]. We report a case of leptospirosis caused by *Leptospira interrogans* serovar *icterohaemorrhagiae* in which unexpected results of a muscle biopsy suggest a mechanism for the occurrence of muscle injury.

A 63-year-old woman from Trinidad returned from a three-week vacation in that country. One week later, she experienced abdominal pain, nausea, vomiting, thigh and calf pain, generalized weakness, and pigmenturia.

The patient was hospitalized on the fourth day of her illness. She was icteric, had gastrointestinal bleeding, and was afebrile. Her abdomen was rigid, all muscle groups were tender, and her thigh and calf muscles were intensely swollen. All upper-extremity muscle groups were Medical Research Council grade 3/5 in strength, and lower extremity muscle groups were grade 0/5, proximally and grade 3/5, distally. Deep tendon reflexes were reduced in the upper extremities and absent in the lower extremities. Babinski responses were absent, and the remainder of the neurological exam was normal.

The patient's hematocrit was 32.5%, and she had a WBC count of 13,700/mm^3. Her serum creatinine level was 5.5 mg/dl; total bilirubin, 25.2 mg/dl (direct, 20.4 mg/100 ml); SGOT, 312 U/liter; SGPT, 164 U/liter LDH, 1,024 U/liter; and her serum creatine phosphokinase (CPK) level was 4,400 U/liter (normal, <170 U/liter). Her urine contained red blood cell casts and myoglobin.

The day after her admission, flat violaceous papules were seen on the patient's arms and legs, and conjunctival suffusion was noted. Bleeding gastric and duodenal ulcers were treated with multiple blood transfusions, and the patient's condition stabilized. Renal failure caused by myoglobin-induced acute tubular necrosis responded to hydration and treatment with mannitol and furosemide. Suspected abdominal sepsis and *Klebsiella* urosepsis was treated intravenously with three days of ampicillin, penicillin, and tobramycin and with 10 days of cefotaxime.

On the eighth day of the patient's illness, a biopsy of the left vastus lateralis muscle was performed. Numerous necrotic muscle fibers were seen, but no evidence of vasculitis or myositis was noted. Leptospirosis was considered in the differential diagnosis and was confirmed by Dieterle silver staining of the muscle biopsy specimen. In addition, samples of blood drawn for serological studies on the eighth day of hospitalization were positive for antibodies to *interrogans* serovar *icterohaemorrhagiae* (titer, 1:1,600 by microscopic agglutination testing). Repeat titers were positive two weeks and two months later. Positive, though much reduced, cross-reactions to other serogroups of *Leptospira* (Canicola, Bataviae, and Ballum) were also seen. This finding is characteristic of early infection. Cultures of urine were negative for *Leptospira*.

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Please address requests for reprints to Dr. Roger W. Kula, Department of Neurology, Box 1213, SUNY Health Sciences Center at Brooklyn, Brooklyn, New York 11203.

The patient could walk without muscle pains with a walker after one month. Her CPK level returned to normal, and following an intensive rehabilitation program, she was discharged five months after the onset of her illness. She could walk independently, though she was mildly weak and areflexic in her lower extremities.

Elevation of the CPK level in a febrile patient with jaundice or uremia may suggest a diagnosis of leptospirosis [2]. Significant, acute muscle injury occurs in 40%–50% of patients with Weil's disease. Among persons with the disease, elevated levels of CPK are seen almost exclusively in those with the severe forms of leptospirosis [3, 4]. In a large series of icteric patients hospitalized for leptospirosis in Salvador, Brazil, the CPK was elevated in 29 (48%) of 61 patients in whom it was assessed. The highest value was 900 U/liter (normal, <170 U/liter). The calf muscles are most commonly affected, but pectoral, back, and abdominal muscles may also be involved. This can lead to misdiagnosis of the condition as an "acute abdomen" [5]. Guedes E. Silva et al. [6] found intramuscular leptospires in six of 23 biopsy samples of gastrocnemius muscle. They felt, however, that skeletal muscle necrosis associated with intramuscular hemorrhage was a more-significant feature of the specimens. Arean [1] reported similar findings in sections of upper-arm and thigh muscle obtained at autopsy.

Our findings from the muscle biopsy specimen obtained early in the course of muscle injury emphasize the importance of direct spirochetal invasion of muscle cells as a primary mechanism in muscle cell injury. Numerous necrotic muscle fibers and basophilic and regenerating myoblasts were found without evidence of hemorrhagic infiltrates or vasculitis. Most of the small intramuscular vessels were unremarkable; several were surrounded by a minimal infiltrate of lymphocytes and plasma cells. A few muscle fibers with vacuoles of various sizes were present and therefore indicated early muscle damage. After staining with a modified Dieterle method (impregnation with silver) we found leptospires within both intact and vacuolated muscle fibers (figure 1). The organisms were not found in necrotic fibers. This finding suggests that the organisms gain access to the cell and cause injury leading to necrosis. Further support for direct muscle injury by leptospires comes from the clinical observation that CPK levels and symptoms of muscle damage usually diminish as the septicemic stage ends in the second week of illness [2]. In the case we report, the biopsy specimen was obtained early in the second (immune) stage: vessels appeared normal and inflammatory changes were limited to a few intramuscular phagocytes. This finding and other pathological evidence showing that the outcome of the muscle disease is healing without scarring or fibrosis [5] support the view that a secondary immune response does not contribute to muscle damage in leptospirosis. Although infection or injury of vascular endothelial cells may play some role in initiating or sustaining muscle cell damage, the more-important pathogenetic mechanism seems to be direct invasion or infection of muscle cells.

Another presumptive mechanism of pathogenicity could be the elaboration of a cellular toxin. Several bacterial infections known to cause muscle injury are acute multisystem illnesses mediated by known toxins: gram-negative endotoxin, staphylococcal endotoxin, and toxins of *Legionella*. Similarities between the clinical and generalized histopathologic findings observed in Weil's disease and those seen in endotoxemia (hemorrhage, hypotension, thrombocytopenia, and ischemic lesions) suggest that a toxin

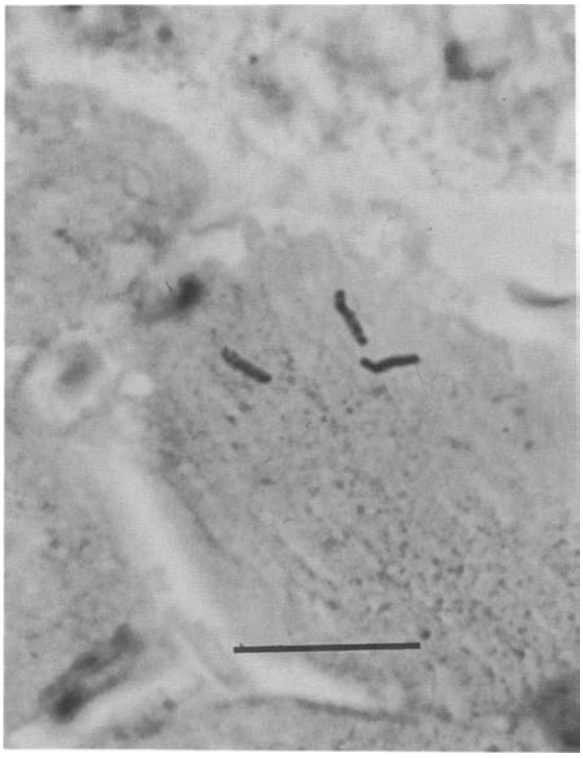

Figure 1. Paraffin cross section of muscle biopsy specimen with *Leptospira* organisms present in intact muscle fibers. Dieterle silver stain, *bar* = 20 μm.

or toxins may be reponsible for some of the pathogenic action of leptospires [7, 8].

The bioassays used in the search for a toxin in leptospirosis have yielded inconclusive results. Hemolysin production was observed in *L. pomona* cultures [9], and a heat-stable substance from sonically disrupted serovar *icterohaemorrhagiae* was noted to cause skin necrosis when injected intradermally into animals [10]. Methods used for the extraction and isolation of endotoxin from gram-negative bacteria have also been applied to leptospires, but injection of the resulting extracts into experimental animals failed to produce any toxic effects [7, 8]. A toxin has not yet been characterized or isolated. Even if leptospires contain no typical endotoxin or exotoxin, the organism may contain proteins or polysaccharides that may be toxic intracellularly.

MARYLOU V. SOLBRIG, JOANNA H. SHER, ROGER W. KULA
Departments of Neurology and Pathology, SUNY Health Sciences Center at Brooklyn, Brooklyn, New York

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