CASE STUDY

A 47-YEAR-OLD MAN WITH TYPE 1 DIABETES, A TENDER SWOLLEN CALF, AND ACUTE ON CHRONIC RENAL IMPAIRMENT

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BACKGROUND

A 47-year-old man with type 1 diabetes mellitus with acute-onset pain and swelling in the right calf, in addition to deterioration in his renal function, is admitted to the renal ward in a university teaching hospital after a referral from his general practitioner. The patient had felt dizzy and lethargic and has been vomiting for 2 days.

MEDICAL HISTORY

The patient was diagnosed with type 1 diabetes mellitus in 1970 with subsequent complications, including bilateral proliferative retinopathy requiring extensive laser photocoagulation therapy, diabetic neuropathy with bilateral Charcot arthropathy of the feet, and plantar ulceration. He has known diabetic nephropathy with a serum creatinine of 3.03 mg/dL. He suffers from hyperlipidemia, hypertension, frequent hypoglycemic episodes, and loss of hypoglycemia awareness.

CURRENT MEDICAL TREATMENT

The patient’s current medical treatment includes insulin aspart, 8 to 10 units per meal; insulin glargine (R-DNA origin) injection, 16 units daily; lisinopril, 30 mg; candesartan cilexetil, 8 mg; furosemide 80 mg; atenolol, 50 mg; amlodipine besylate, 10 mg; doxazosin XL, 16 mg; atorvastatin calcium, 10 mg; aspirin, 75 mg; intravenous iron; and subcutaneous erythropoietin.

REVIEW OF SYSTEMS

The patient had no rashes, bruising, bleeding, headaches, fever, or chills. He had no visual disturbances or seizures. He had experienced shortness of breath over the past few months, especially with exertion. He felt nauseous and had vomited several times before admission. There was no change in bowel movements, although he noted diminished appetite over the past few weeks. He had no dysuria or hematuria.

FAMILY HISTORY

The patient’s father died at age 72 years from a myocardial infarction, and his mother died at age 58 years from disseminated breast carcinoma. He has no siblings.

SOCIAL HISTORY

The patient was born and raised in Manchester, Great Britain, and previously worked as a mail carrier postman. He is married and has 3 children. He ceased smoking 10 years ago and occasionally drinks alcohol.

PHYSICAL EXAMINATION

At this presentation, the patient appeared to be alert. Physical examination revealed the following findings: weight, 94 kg; blood pressure (supine), 118/62 mm Hg; blood pressure (standing), 96/50 mm Hg; heart rate, 55 beats/minute and regular; respiratory rate, 20 breaths/minute; and body temperature, 37.1°C. No jaundice, cyanosis, or finger clubbing. Patient has multiple tattoos.

The patient has early peripheral cataracts in both eyes. Dilated fundoscopy demonstrated extensive laser photocoagulation (Figure 1). The ear, nose, and throat examinations were within the reference ranges. There was no enlargement of the thyroid and no lymphadenopathy.

His pulse was regular, with a bradycardia of 55 beats/minute. The jugular venous pressure was not elevated, and there were no cardiac murmurs indicated by auscultation of the precordium. There was no pedal edema.
Right and left hemithoraces were resonant to percussion, and breath sounds were normal.

Abdominal examination revealed a nontender abdomen with normal bowel sounds and no hepatosplenomegaly.

Examination of the patient’s lower limbs demonstrated a tender swelling over the posteromedial aspect of the right calf. The right calf had a maximal circumference of 53 cm and the left calf 40 cm. He had bilateral Charcot joints of the ankles (Figure 2) with a plantar ulcer (Figure 3) on his right foot. He had good pedal pulses. There was a severe sensory/motor neuropathy evidenced by loss of sensation to touch, pinprick, and vibration sense to the knees with absent knee and ankle reflexes.

**DIAGNOSIS ON HOSPITAL ADMISSION**

The patient was admitted to the hospital with a diagnosis of possible right deep venous thrombosis and acute on chronic deterioration of renal function. Laboratory tests (abdominal and calf ultrasound examination followed by diagnostic magnetic resonance [MR] and computed tomography-guided biopsy) were performed.

**LABORATORY STUDIES**

Laboratory tests revealed the following serum values: sodium, 140 mmol/L (132–144); potassium, 5.3 mmol/L (3.5–5.5); urea nitrogen, 96.6 mg/dL (10–21); creatinine, 5.4 mg/dL (0–1.2); bicarbonate, 20 mmol/L (24–30); calcium, 10.0 mg/dL (8.4–10.8); phosphate, 4.6 mg/dL (2.2–4.3); cholesterol, 155 mg/dL (70–200); high-density lipoprotein, 54 mg/dL (30–70); triglycerides, 106 mg/dL (70–160); bilirubin, 1.2 mg/dL (0–1.3); alanine aminotransferase serum, 419 U/L (70–330; isoenzyme-hepatic); creatinine kinase, 380 U/L (0–190); hemoglobin (Hb), 10.9 g/dL (13–18); mean corpuscular volume, 88 fl (80–97); white blood cell count, 7.9 x 10^9/L (4–11); platelets, 170 x 10^9/L (150–400); folate, 5.6 µg/L (3–16); B12, 310 ng/L (150–900); and ferritin, 41.3 µg/L (15–200).

The immunology report revealed the following findings: erythrocyte sedimentation rate (ESR), 58 (0–5); C-reactive protein, less than 3; CH50, 100% in the reference range (80–180); C3, 98 mg/dL (62–160); C4, 21 mg/dL (14–39); immunoglobulin (Ig) G, 12.2 g/L (5.9–15.6); IgA, 3.9 g/L (0.6–5.0); IgM, 2.0 g/L (0.4–2.3); electrophoresis, in the reference range; antineutrophil cytoplasmic antibody, negative (-ve); antibody to glomerular basement membrane, 1 U (<30); rheumatoid factor, less than 8 IU (<8); antinuclear antibody, negative (-ve).

A test of the patient’s glycemic control revealed a value of HbA1c, 7.4% (4.5–6.5). His cumulative HbA1c from 1996 to 2002 was 10.2 ± 1.4%. Only in 2003 was glycemic control improved to achieve HbA1c of 7.3 ± 0.2%.

**Figure 1. Normal Optic Disc, Retinal Vessels, and Macula**

Retinal photograph of patient demonstrating a normal optic disc, retinal vessels, and macula with previous photocoagulation (→) for macular edema with fibrosis (→).

**Figure 2. Typical Diabetic Neuropathic Feet**

Typical diabetic neuropathic feet with clawing of toes and bilateral mid-foot Charcot (→) with a dorsal scar on left foot from previous surgery.
Renal function showed the creatinine level at 5.39 mg/dL and the 24-hour urine protein at 4.17 g/period.

Abdominal ultrasound examination demonstrated a healthy gallbladder, pancreas, and spleen and a fatty liver. Both kidneys were within reference range and outlined with some thinning of the cortex but no evidence of a focal renal mass, calculi, or obstruction.

Calf ultrasound examination excluded deep venous thrombosis, although edema was noted in the swollen area.

An MR scan using coronal and axial T1-weighted spin echo, sagittal T2-weighted fast field echo, and axial fat suppressed T2-weighted turbo spin echo sequences was performed on the right calf. The examination demonstrated an extensive high-signal abnormality on the T2-weighted sequence, throughout the medial head of the gastrocnemius muscle and surrounding adjacent tissue planes (Figure 4). Images appeared to be a gross myositis with edema and hemorrhage in and around the muscle. No abscess was identified, but there were areas of heterogeneity that may have represented muscle necrosis or focal hemorrhage.

Computed tomography-guided biopsy was performed of the representative area of the right gastrocnemius muscle, using a 14-gauge Tru-cut needle with a single pass.

A biopsy report by Professor T. Freemont, Osteoarticular Pathology, was as follows: the biopsy contained inflamed skeletal muscle with a severe active chronic inflammatory cell infiltrate present between individual myocytes (Figure 5A), showing varying degrees of necrosis, characterized by loss of cross striations and nuclei (Figure 5B) with fragmentation. Cellular debris, including nuclear dust, was associated with the infiltrate. The inflammatory cell infiltrate consisted predominantly of neutrophils, many of which had undergone leukocytoclasis. There was no evidence of an active vasculitis. No granuloma or microorganisms were identified.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of a mass with inflammatory features includes neoplasia, infection, ischemia, trauma, and vasculitis. More specifically, deep vein thrombosis, acute exertional compartment syndrome, muscle rupture, soft-tissue abscess, hematoma, sarcoma, inflam-
matory or calcifying myositis, and pyomyositis must be considered.

Soft-tissue sarcomas of the leg often occur in the thigh and are typically painless. The site of swelling and elevated sedimentation rate in this patient do not indicate a soft-tissue sarcoma.

Penetrating trauma can cause a false aneurysm. Blunt trauma can result in myositis ossificans, a benign, ossifying soft-tissue mass within skeletal muscle that simulates an inflammatory or neoplastic lesion.

Granulomatous lesions, such as those lesions associated with cat scratch fever, sarcoidosis, and tuberculosis, rarely present as a soft-tissue mass in the leg.

Pyomyositis, a deep bacterial (Staphylococcus aureus 90%) abscess of the skeletal muscle often occurs in proximal muscles. Patients present with local muscle pain, swelling, and tenderness, with or without fever associated with a leukocytosis and elevated sedimentation rate. Despite extensive myonecrosis, serum levels of muscle enzymes are often normal or only slightly elevated.

Muscle infarction is rare, but it has been reported in long-duration type 1 diabetes mellitus and in poor glycemic control complicated by nephropathy, neuropathy, and hypertension. An abrupt onset of severe pain occurs in the quadriceps, thigh adductors, or hamstrings in the absence of trauma or fever. Laboratory tests typically show a white blood cell count in the reference range with slightly elevated or reference levels of creatinine kinase. The MRI scan typically demonstrates marked muscle edema (abnormally high signal intensity on T2-weighted images) with edema in the adjacent subcutaneous and perifascial tissues. Arteriolar thrombosis has been postulated to have a major role in diabetic muscle infarction.

Statin-induced myositis: statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) are associated with skeletal muscle complaints, including clinically important myositis and overt rhabdomyolysis. Muscle pain and weakness may affect 1% to 5% of patients and the US Food and Drug Administration MedWatch Reporting System lists 3339 cases of statin-associated rhabdomyolysis reported between 1990 and 2002. The risk of myositis/rhabdomyolysis with statin use is exacerbated in patients with compromised hepatic and renal function, hypothyroidism, diabetes mellitus, and concomitant use of the fibrate gemfibrozil that increases statin plasma concentration.

The mechanism of skeletal muscle injury is unclear, although recent evidence suggests that statins reduce the production of small regulatory proteins that are important for myocyte maintenance.

HOSPITAL COURSE

The patient was rehydrated with intravenous fluid. His renal function improved but did not return to previous baseline levels (sodium, 141 mmol/L [132–144]; potassium, 5.1 mmol/L [3.5–5.5]; urea nitrogen 83.7 mg/dL [10–21]; creatinine, 3.96 mg/dL [0–1.2]). Other abnormalities, which included the raised phosphate and normochromic normocytic anemia, were attributed to diabetic nephropathy.

The raised alkaline phosphatase, with the demonstration of fatty liver on ultrasound examination, was...
attributed to nonalcoholic steatohepatitis that has been related to obesity, type 2 diabetes mellitus, hyperlipidemia, and pregnancy. Oxidative stress and lipid peroxidation are implicated in its pathogenesis.

**OUTPATIENT COURSE**

With appropriate analgesia and rest, the tenderness and swelling over the patient's right calf improved over a 3-week period. Repeated relevant laboratory investigations demonstrated the following levels: sodium, 141 mmol/L (132–144); potassium, 5.1 mmol/L (3.5–5.5); urea nitrogen, 73.9 mg/dL (10–21); creatinine, 3.27 mg/dL (0–1.2); creatinine kinase, 186 U/L (0–190); ESR, 16 (0–5).

**DIAGNOSES AND MANAGEMENT**

The patient was diagnosed as having diabetic skeletal-muscle infarction and prerenal decompensation of established diabetic nephropathy. The treatment of diabetic muscle infarction is supportive and often includes the administration of analgesics and short-term immobilization of the involved leg. The short-term prognosis is excellent because the symptoms resolve spontaneously over a period of several weeks to months. However, contralateral or recurrent lesions may develop in almost 50% of patients. The deterioration in renal function was attributed primarily to the episode of nausea and vomiting with resultant hypotension, as evidenced by the significant postural hypotension on hospital admission that led to prerenal decompensation of established renal impairment secondary to diabetic nephropathy. Classically, rhabdomyolysis accounts for 5% to 15% of cases with acute renal failure (acute tubular necrosis) caused by myoglobin overload, hypovolemia, and acidosis associated with creatinine kinase greater than 16,000 units/L. In the case of this patient’s occurrence of skeletal-muscle necrosis, the physician must consider a minor contributory role of this mechanism leading to decreased afferent renal blood flow and partial renal tubular obstruction in kidneys that are already compromised because of established diabetic nephropathy.

**REFERENCES**