Acute Renal Failure and Myalgia in a Transplant Patient

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ABSTRACT
A 64-yr-old man with kidney transplant for ESRD as a result of diabetic nephropathy presented with acute renal failure, weakness, myalgia, and pigmented urine. His medications included mycophenolate, cyclosporine, prednisone, furosemide, diltiazem, aspirin, simvastatin, an angiotensin receptor blocker, and insulin. A renal biopsy was performed. Pathologic findings and differential diagnosis are discussed, and the literature is reviewed.


CLINICAL HISTORY

A 64-yr-old whiteman with a kidney transplant presented in August 2006 for evaluation of 1-wk history of weakness and myalgia. Muscle aches and weakness started in the lower legs and spread to the anterior thigh and calf. The pain rendered him unable to walk. He had diarrhea for 3 d and noticed red/brown urine but maintained normal urine output.

He had received a living, nonrelated, zero-antigen match kidney in June 2005 for ESRD as a result of diabetic nephropathy and had been in stable health, with controlled glucose and moderately controlled BP but persistent hyperlipidemia. He had one episode of acute cellular rejection in January 2006, with stable serum creatinine (2.6 to 2.7 mg/dl). His medications included mycophenolate, cyclosporine, prednisone, furosemide, diltiazem, aspirin, simvastatin, and insulin. An angiotensin receptor blocker (ARB) was added, and diuretic dosage was increased in mid-July 2006, when he presented with edema and weight gain but stable creatinine.

His medical history was significant for no alcohol use and 60 to 70 pack-years of smoking, but he had quit 5 yr previously. He had four-vessel coronary artery bypass in 2000, implantable cardioverter defibrillator placement in March 2005, and elective cholecystectomy in 2005.

His BP was 152/78 mmHg, temperature was 97.6°F, pulse was 88 beats/min, weight was 259 lb, and body mass index was 36.1. He had tenderness and 1+ edema of the lower extremities but otherwise normal examination. Admission laboratories (normal in parentheses) showed sodium 130 mmol/L, potassium 7.0 mmol/L, chloride 95 mmol/L, CO₂ 19 mmol/L, serum creatinine 8.3 mg/dl, blood urea nitrogen 143 mg/dl, glucose 242 mg/dl, phosphorus 8.8 mg/dl, aspartate transaminase 503 U/L, alanine transaminase 204 U/L, alkaline phosphatase 80 U/L, total bilirubin 0.6 mg/dl, direct bilirubin 0.4 mg/dl, and uric acid 7.8 mg/dl. Hematocrit was 31.5%, platelets were 209,000/mm³, white blood cell count was 8900/mm³, lymphocytes were 5.3%, polymorphonuclear leukocytes were 88.5%, monocytes were 5.6%, eosinophils were 0.5%, and basophils were 0.1%. Prothrombin time and partial thromboplastin time were normal. Total creatine kinase (CK) was 16,393 U/L (21 to 232) with CK-MB 123.9 ng/ml (0 to 3.6). CK-MM was not directly measured. Urinalysis showed no red or white blood cells and positive dipstick for protein, large blood, and urobilinogen, with negative glucose and bilirubin.

An ultrasound of the transplanted kidney was unremarkable, with no signs of obstruction. He was admitted and treated with fluids and cyclosporin. ARB and simvastatin were discontinued, and the patient was given Imuran. On day 4, with creatinine remaining high, a renal biopsy was performed.

Renal Biopsy Findings
Light microscopic examination showed 18 intact glomeruli with mild increase in mesangial matrix and cellularity. The glomerular basement membranes were unremarkable. There was approximately 5% tubulointerstitial fibrosis, mostly in the subcapsular areas and mild interstitial lymphocytic infiltrate with rare tubulitis in scarred areas.

Published online ahead of print. Publication date available at www.jasn.org.

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and rare interstitial neutrophils and eosinophils. There was no lymphocytic infiltrate or tubulitis in the nonscarred cortex. Tubules were focally dilated with extensive epithelial cell flattening and sloughing, surrounded by mild interstitial edema. There were frequent intratubular reddish-brown granular casts with occasional cell debris (Figure 1A). None of these casts had a fractured appearance or surrounding syncytial reaction. There were no viral cytopathic changes. Arterioles showed mild hyalinosis. Interlobular arteries showed mild to moderate intimal fibrosis with no endothelialitis. Casts showed strong positivity with specific immunoperoxidase staining for myoglobin (with an antibody without cross-reactivity with hemoglobin; Figure 1B). Immunofluorescence showed only trace focal segmental mesangial and capillary loop staining for IgG and polyvalent antisera. Electron microscopic examination showed mild segmental expansion of lamina rara interna of the glomerular basement membrane and mild segmental increase in mesangial matrix, without any deposits. Several tubular profiles contained globular casts with dark central core and slightly lighter periphery and no substructure, accompanied by tubular cell vacuolization, loss of brush borders, and sloughing (Figure 1C).

**Pathologic Diagnosis**
The presence of extensive tubular epithelial cell injury with granular reddish-brown casts by light microscopy and dark granular casts by electron microscopy is characteristic of myoglobin-induced acute tubular injury (ATI), confirmed by immunohistochemistry.

**DISCUSSION**
There are many causes of acute renal failure (ARF) in the transplant. Common etiologies include acute rejection, calcineurin inhibitor toxicity and ATI. In specific clinical circumstances, additional considerations, such as acute vasoconstriction or hypoperfusion (related to e.g. volume depletion), drug hypersensitivity reaction, infection (particularly viral), obstruction, thrombotic microangiopathy (drug-related, idiopathic or recurrence of original disease), may be involved. The renal biopsy is essential in establishing the precise cause of ARF in the graft. Most of these conditions have distinct morphologic lesions, which allow precise diagnosis of the underlying process, which may then direct appropriate treatment.

In our patient, the clinical differential diagnoses included acute ischemic injury due to volume depletion due to history of diarrhea, calcineurin inhibitor toxicity or possibly rhabdomyolysis. The renal morphologic findings showed characteristic myoglobin-induced ATI.

The differential diagnosis of prominent casts includes ATI as a result of ischemia, with Tamm-Horsfall casts, which must be distinguished from the characteristic brownish-pigmented myoglobin casts of rhabdomyolysis. Pigmented intratubular casts may also be seen with hemoglobinuria. Hemoglobinuria may occur with acute hemolysis as a result of, for example, incompatible blood transfusion, malaria, quinine ingestion, or paroxysmal hemoglobinuria. An additional rare consideration in the differential diagnosis of pigmented intratubular casts is bile casts. Typically, tubular injury develops with bilirubin levels >20 mg/dl, in combination with hypoalbuminemia or endotoxemia. Rarely, renal biopsies have been performed in this clinical setting, revealing intratubular casts with bilirubin pigment. Specific immunostaining is helpful in differentiating these casts from myoglobin casts. Differentiation of myoglobinuric versus hemoglobinuric injury may also be done by examination of the patient’s blood and urine. Circulating myoglobin, in contrast to hemoglobin, is not highly protein bound and is readily filtered into the urine. Thus, rhabdomyolysis rarely results in serum myoglobin concentrations >25 mg/L, whereas serum discoloration occurs when concentrations are >100 mg/L. Therefore, light pink discoloration of serum is very unusual in rhabdomyolysis and should suggest additional hemolysis. Both myoglobin and hemoglobin can be detected in the urine with a dipstick test, using the orthotoli-

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**Figure 1.** (A) Myoglobin casts (arrows) with a reddish-brown granular appearance, associated with tubular epithelial cell injury (hematoxylin and eosin stain). (B) Myoglobin casts stain brown with immunoperoxidase and antimyoglobin antibody. (C) A myoglobin cast within a tubule with characteristic dark globular appearance and slightly lighter periphery (transmission electron microscopy). Magnifications: ×400 in A and B; ×50,000 in C.
dine reaction, which reacts with the heme molecule and therefore cannot differentiate between these two conditions. This point is illustrated in this case, in which, although there was no hematuria by microscopic examination, the dipstick test was positive for large blood in urine.

Intratubular casts are also an essential component of light-chain cast nephropathy (LCCN). These casts typically have a fractured appearance and surrounding syncytial cell reaction and frequently but not always show light chain–restricted staining by immunofluorescence. However, LCCN is uncommon in the transplant, although it may occur. Rapamycin caused ATI accompanied by intratubular casts with very similar appearance to those seen in LCCN. However, the casts were composed of keratin, representing remnants of degenerated epithelial cells rather than monoclonal light chains.

Rhabdomyolysis is characterized by severe muscle destruction and myoglobinuria. Muscle biopsy findings include loss of cross-striations and nuclei of myocytes and partial regeneration and a lack of inflammatory cell infiltrate. Contents of damaged myocytes, including myoglobin and CK, are released into blood. A rise in serum myoglobin level precedes an increase in serum CK. The half-life of myoglobin is only 1 to 3 h, and its concentration usually returns to normal levels 1 to 6 h after the injury as a result of its rapid clearance through kidneys or its metabolism to bilirubin. Cell membrane defects, mitochondrial dysfunction, impaired myocyte duplication.

Rhabdomyolysis is estimated to underlie approximately 5 to 25% of all cases of ARF. ARF is the most serious complication of rhabdomyolysis and occurs in up to 16.5% of patients with myoglobinuria. Drugs and alcohol are the most common (up to 81%) causes of rhabdomyolysis (Table 1). Other causes include toxins (including illicit drugs), trauma, excessive exercise, long-term immobility, hereditary muscle enzyme defects, infections, metabolic/endocrine disorders, and hypo/hyperthermia. The classic presenting features of rhabdomyolysis include muscle injury and/or pain, pigmented urine, and renal dysfunction. However, in drug-induced rhabdomyolysis, other symptoms may predominate the clinical findings and therefore

Table 1. Selected medications and mechanisms associated with rhabdomyolysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanisms</th>
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</thead>
<tbody>
<tr>
<td>lovastatin, simvastatin, pravastatin, cerivastatin, etc.</td>
<td>Cell membrane defects, mitochondrial dysfunction, impaired myocyte duplication</td>
</tr>
<tr>
<td>gemfibrozil</td>
<td>Glucuronidation pathway (interaction with statins)</td>
</tr>
<tr>
<td>bezafibrate, clofibrate, ciprofibrate, clofibrate, fenofibrate</td>
<td>Unknown</td>
</tr>
<tr>
<td>ezetimibe</td>
<td>Unknown</td>
</tr>
<tr>
<td>macrolides (e.g., erythromycin)</td>
<td>Cytochrome P450 inhibition (interaction with statins)</td>
</tr>
<tr>
<td>azole antifungals (e.g., itraconazole)</td>
<td>Cytochrome P450 inhibition (interaction with statins)</td>
</tr>
<tr>
<td>amphotericin B</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>Hypersensitivity reaction</td>
</tr>
<tr>
<td>haloperidol, lithium, benzodiazepines, cyclic antidepressants, antihistamines, glutethimide, barbiturates</td>
<td>Prolonged immobilization, muscle compression, ischemia</td>
</tr>
<tr>
<td>thiazides, cathartic agents</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>cocaine</td>
<td>Prolonged vasoconstriction, trauma, direct cytotoxicity</td>
</tr>
<tr>
<td>LSD, phencyclidine, ecstasy</td>
<td>Prolonged muscle contraction</td>
</tr>
<tr>
<td>narcotics, benzodiazepines</td>
<td>Prolonged immobilization, muscle compression, ischemia</td>
</tr>
<tr>
<td>ethanol</td>
<td>Prolonged immobilization, trauma, direct myocytotoxicity</td>
</tr>
<tr>
<td>diltiazem, verapamil, amiodarone, mibebradil</td>
<td>Cytochrome P450 inhibition (interaction with statins)</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>Cytochrome P450 inhibition (interaction with statins)</td>
</tr>
<tr>
<td>corticosteroids</td>
<td>Direct cytotoxicity</td>
</tr>
<tr>
<td>tacrolimus</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Statins effectively reduce hyperlipidemia and its related cardiovascular risk, both of which are increased in transplant patients. Both corticosteroids and cyclosporine can worsen hyperlipidemia, further increasing cardiovascular risk. Moreover, experimental studies suggest that statins may be beneficial through lipid-independent mechanisms, such as improving endothelial function, reducing proinflammatory cytokines and adhesion molecules, upregulation of endothelial nitric oxide synthase, antioxidant effects, and some immunomodulatory properties. The postulated beneficial effects of statins on acute cellular or vascular rejection remain controversial. The mechanisms of statin-induced muscle damage are unknown, but hypotheses include defects in cell membrane structure by blocking cholesterol synthesis, mitochondrial dysfunction by reducing isoprenoids, such as ubiquinone, and impaired myocyte duplication.

Experimental studies suggest that myoglobinuria alone is insufficient to induce ARF and that additional hypovolemia, renal vasoconstriction, or urine acidification is required for nephrotoxicity. The proposed mechanisms of myoglobinuria-associated ARF include obstruction by casts, tubulotoxic effect of ferrihemate, a breakdown product of myoglobin at pH <5.6, and renal vasoconstriction secondary to inhibition of nitric oxide synthesis. To our knowledge, direct nephrotoxicity of statins has not been systematically studied. Nevertheless, findings suggestive of direct renal tubular toxicity on high-dosage statin therapy without rhabdomyolysis was reported in a patient with familial hypercholesterolemia.

Current therapeutic modalities include withdrawal of myotoxic agents, intravenous volume expansion, urinary alkalinization, and forced diuresis. Prognosis of rhabdomyolysis depends on severity and comorbid conditions, with mortality of 52% in patients with ARF, compared with 14% in those without ARF, in a series of critically ill intensive care units. A subclinical presentation of rhabdomyolysis without these common features may be overlooked.

Rhabdomyolysis is an important but rare adverse effect of statins. The incidence of all myotoxic effects of statins in the general population is between 1 and 7%, most of which are myalgias that are reversible within 2 to 3 wk after statin withdrawal. Fatal rhabdomyolysis after statins is very rare, with a reported rate to the Food and Drug Administration per 1 million prescriptions among all patients of 0.00 for fluvastatin, 0.04 for pravastatin, 0.12 for simvastatin, and 0.19 for lovastatin. Importantly, statins have interactions with other drugs, and their metabolism is affected by the major hepatic cytochrome P450 isoenzyme CYP3A4 (Figure 2). Cyclosporine and clarithromycin are CYP3A4 inhibitors and thereby increase statin levels, such that patients receiving either of these drugs in addition to statins that are metabolized by CYP3A4 enzymes, including simvastatin, lovastatin, atorvastatin, and cerivastatin (withdrawn in 2001), have increased risk for myotoxicity. Gemfibrozil does not inhibit the P450 system but increases the risk for statin-induced rhabdomyolysis through the glucuronidation pathway. Fenofibrate, which does not interfere with glucuronidation, is associated with less myotoxicity. Occurrence of rhabdomyolysis in transplant patients has mostly been related to a combination of cyclosporine with either lovastatin or simvastatin. Pravastatin and fluvastatin, because of their different metabolism, are least likely to cause myotoxicity in transplant patients. Fluvastatin, though to be a substrate of the CYP2C9 enzyme, may have an interaction with diclofenac, which is metabolized by the same enzyme. Tacrolimus has been rarely implicated in rhabdomyolysis.

Other reported risk factors for statin-induced myopathy include advanced age; small body size; female gender; renal and hepatic dysfunction; hypothyroidism; diabetes; alcohol abuse; perioperative period; debilitation; large quantities of grapefruit juice; and concomitant consumption of cyclosporine, fibrates, azole antifungals, nitocinic acid (rarely), macrolide antibiotics, HIV protease inhibitors, nefazodone, digoxin, warfarin, verapamil, amiodarone, mibefradil, or diltiazem (Table 1).

Figure 2. Schematic pathways of statin-induced rhabdomyolysis and ARF. ©, competitive inhibition.
care unit patients with rhabdomyolysis. The Clinical Advisory on the Use and Safety of Statins recommends discontinuation of these drugs in patients with rhabdomyolysis but does not provide any guidelines of how to control hyperlipidemia. Rechallenging the patient with another statin is associated with frequent recurrence of muscle symptoms. Fortunately, our patient tolerated reintroduction of statin therapy, as other factors potentiating risk were removed. Ezetimibe, niacin, or fibrates also comparably are associated with myotoxicity when replacing statins in this setting. Therefore, diet remains key in managing hyperlipidemia in these patients. Resins, which have never been reported to cause rhabdomyolysis, may also be considered as a logical alternative for statins.

**DISCLOSURES**

None.

**REFERENCES**


**CLINICAL FOLLOW-UP**

After admission, the patient was given intravenous fluids and cyclosporine, simvastatin, mycophenolate mofetil, furosemide and ARB were stopped, and azathioprine was started. One week later, he had no significant myalgia but still had weakness, CK was <1000 U/L, transaminases were markedly improved, and urine became clear. Serum creatinine decreased to 3.2 mg/dl in 2 wk and to his baseline level of 2.5 mg/dl at 3 mo of follow-up. Ezetimibe was started to control hyperlipidemia in January 2007 but discontinued because of back pain. The patient is currently on simvastatin at the same dosage before rhabdomyolysis with no recurrence of symptoms.

**CONCLUSIONS**

This patient had rhabdomyolysis and myoglobin-induced ATI, most likely secondary to simvastatin. He had additional risk factors for rhabdomyolysis, including cyclosporine, diltiazem, and reduced GFR, possibly with reduced renal blood flow secondary to recent diarrhea, increased furosemide, and ARB. Prompt recognition and diagnosis on the basis of characteristic clinical and pathologic findings with appropriate therapy restored his renal function to baseline. Rhabdomyolysis and myoglobinuric ARF, although rare, are serious complications of statin therapy. Renal transplant patients are at greater risk for these complications as a result of concomitant use of cyclosporine and possible renal dysfunction.