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Daptomycin-induced rhabdomyolysis complicated with acute gouty arthritis

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Abstract

Rhabdomyolysis is a well-documented side effect of daptomycin and is associated with hyperuricemia. However, the occurrence of acute gouty arthritis secondary to rhabdomyolysis-induced hyperuricemia has not been reported. We report a case of a patient who presented with daptomycin-induced rhabdomyolysis prior to the usual 7-10-day administration period. This case was complicated with acute gouty arthritis after 7 days from the onset of rhabdomyolysis symptoms. Treatment consisted of fluid management with the addition of prednisone for gouty arthritis treatment given his poor kidney function. This report indicates the importance of early monitoring of creatine kinase levels in patients on daptomycin to prevent complications from rhabdomyolysis.

Keywords: rhabdomyolysis, daptomycin, gout, hyperuricemia, acute gouty arthritis

Introduction

Rhabdomyolysis is a potentially fatal condition caused by the breakdown of skeletal muscle and the subsequent release of intracellular muscle components into the circulation and extracellular space. An elevated creatine kinase (CK) level is the most accurate laboratory test for diagnosing this condition. Clinical manifestations can range from no symptoms with raised CK levels, to myalgia, weakness, and myoglobinuria, to acute renal failure with significantly elevated CK levels and electrolyte disorders. It may result from direct muscular injuries, muscle overuse, infections, hereditary conditions, and the use of specific drugs. Daptomycin is a lipopeptide antibiotic and has been linked to an increased risk of rhabdomyolysis, particularly at

high doses. The cornerstone of the treatment is volume expansion and correction of any electrolyte abnormalities.

Case presentation

A 74-year-old man with a past medical history of type 2 diabetes mellitus, hypertension, hypothyroidism, hyperlipidemia, and stage 3 chronic kidney disease presented with a three-day history of severe myalgias, generalized weakness, and oliguria. He was recently admitted a week ago with right elbow pain and swelling. Arthrocentesis was done at that time, and the synovial fluid showed a white blood cell (WBC) of 70,270/mm^3 with cloudy color. Calcium pyrophosphate crystals were present without monosodium urate crystals. He was treated for a septic right elbow with incision and drainage, a washout procedure, and intravenous antibiotics. He was discharged on a 6-week course of intravenous daptomycin 8mg/kg and oral levofloxacin 750 mg daily. He denied any other medical or surgical history of joint diseases and denied having fevers, hematuria, dysuria, or recent trauma. His drug history included lisinopril 20 mg, hydrochlorothiazide 12.5 mg, and atorvastatin 20 mg daily; he has been compliant for years with no recent dose changes.

On physical examination, there were no signs of redness, swelling, or erythema of any joint, including the right elbow incision from the washout procedure during the last admission. The bedside urinal contained dark yellow urine. Laboratory tests showed blood urea nitrogen of 63 mg/dL, creatinine of 2.7 mg/dL increased from a baseline of 1.2 mg/dL, myoglobin of 7,780 ng/mL, and CK of 10,719 international units/L. The CK increased to 26,250 international units/L

the next day. He was admitted to the hospital for acute kidney injury and rhabdomyolysis, and intravenous fluids were started. On hospital day four, he developed severe left knee pain that worsened with movement. There was a significant effusion with warmth presented on examination. On hospital day five, additional pain in the left thenar prominence was reported.

A four-view x-ray of the left knee showed chondrocalcinosis in the medial and lateral compartments of the knee joint consistent with calcium pyrophosphate deposition or pseudogout (Figure 1). Three-view x-ray of the left hand showed periarticular bony erosions consistent with gout (Figure 2). Left knee arthrocentesis was done, and fluid analysis revealed monosodium urate and calcium pyrophosphate crystals without bacterial growth. His uric acid was elevated at 10.7 mg/dL; it was previously normal a week ago. A rheumatoid factor, anti-nuclear antibodies, and cyclic citrulline peptide levels were negative.

His routine medicines, including lisinopril and hydrochlorothiazide, were held, and nephrotoxic medications were avoided. Daptomycin was discontinued based on the concern of daptomycin-induced rhabdomyolysis. Levofloxacin was also discontinued, and intravenous ceftaroline 300 mg every 12 hours was started during this admission to continue treatment of the septic arthritis of his right elbow joint. Oral prednisone 40 mg daily was started for acute gouty arthritis treatment without non-steroidal anti-inflammatory drugs due to acute kidney injury. His CK levels trended down, and kidney function improved over the hospital course (Figure 3,4). Ceftaroline was switched to intravenous ceftriaxone 2 g daily and oral levofloxacin 750 mg daily upon discharge due to the high cost of ceftaroline.

Discussion

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic first approved by the United States Food and Drug Administration (FDA) in 2003 for the treatment of complicated skin and skin structure infections in adult and pediatric patients (1 to 17 years of age) and was FDA approved in 2005 for the treatment of *Staphylococcus aureus* bacteremia, including adult patients with right-sided endocarditis.[1,2] It binds to cell membranes causing rapid depolarization and inhibiting the intracellular synthesis of DNA, RNA, and protein.[3] It has bactericidal activity against a wide spectrum of Gram-positive organisms with coverage for *Staphylococcus* spp (including *Staphylococcus aureus* and coagulase-negative *Staphylococcus*), *Enterococcus* spp, *Streptococcus pneumoniae* (including penicillin-resistant strains), and other viridans-group, beta-hemolytic *Streptococcus* spp (*Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus dysgalactiae*), *Corynebacterium* spp, *Leuconostoc* spp, *Pediococcus* spp, and Gram-positive anaerobes (including *Clostridium* spp and *Cutibacterium acnes*).[4] However, FDA did not approve daptomycin for the treatment of pneumonia and *S aureus* left-sided infective endocarditis due to poor outcomes. Moreover, there have been no studies in patients with prosthetic valve endocarditis.

Daptomycin is known to be associated with several side effects, including eosinophilic pneumonia, anaphylaxis/hypersensitivity reaction, myopathy, peripheral neuropathy, potential

nervous and muscular system toxicities in children younger than 12 months, increased international normalized ratio (INR)/prolonged prothrombin time, and rhabdomyolysis.

Rhabdomyolysis

Rhabdomyolysis is a clinical syndrome of skeletal muscle injury characterized by the breakdown and necrosis of muscle tissue causing the release of intracellular contents, including myoglobin, electrolytes, and other sarcoplasmic proteins (e.g., CK, aspartate aminotransferase, alanine aminotransferase, aldolase, and lactate dehydrogenase) into the bloodstream.[6,7] Clinical manifestations range widely from no symptoms to severe life-threatening symptoms and renal failure depending on the severity of muscle damage. Symptoms of muscle necrosis include myalgia, muscle weakness, cramping, muscle swelling, and gross pigmenturia without hematuria. Skin changes occur in a minority of patients with pressure necrosis including blisters or discoloration. Acute kidney injury (AKI) is a consequence of severe rhabdomyolysis and indicates a worse prognosis. Rhabdomyolysis is not only caused by trauma; other causes (causes of rhabdomyolysis are summarized in Table 1) of rhabdomyolysis include strenuous exercise, muscle hypoxemia from prolonged immobilization or major artery occlusion, body temperature-related muscle injury, including heat stroke, malignant hyperthermia, and neuroleptic malignant syndrome, electrolyte disorders including hypokalemia, hypophosphatemia, and hypocalcemia, and infections, including *S aureus* pyomyositis, *Clostridium* spp, and *Streptococcus pyogenes*. Genetic disorders should be suspected in patients who develop rhabdomyolysis in childhood or have recurrent episodes of rhabdomyolysis which are caused by carbohydrate or lipid enzyme deficiency and myopathies leading to ATP delivery

problems. Toxins and medications have been implicated as a cause of rhabdomyolysis; these include heroin, cocaine, amphetamine, snake venom, statins, fibrates, colchicine, and protease inhibitors.[7]

Multiple antibiotics have been associated with rhabdomyolysis. Macrolides and fluoroquinolones were reported to have an association with rhabdomyolysis when used either alone or in combination with a statin. Cefaclor has been associated with rhabdomyolysis when used with non-steroidal inflammatory drugs (NSAIDs). Rhabdomyolysis was also listed as an adverse drug reaction of cefdinir by the US FDA.[9] Liver disorders are a possible risk factor for rhabdomyolysis with meropenem use.[10] A recent study reported an increased rate of rhabdomyolysis in male hematopoietic cell transplantation recipients taking sirolimus with trimethoprim-sulfamethoxazole.[11] Knowing these side effects is crucial to monitor CK levels since rhabdomyolysis can be fatal.

Rhabdomyolysis has developed in 5% of patients who received daptomycin, and myopathy was identified in 2 to 14 % of patients. This occurs more commonly at a higher dose (8mg/kg/day) than the standard dose (6 mg/kg/day) and in patients who had dose intervals shorter than 24 hours. The risk of rhabdomyolysis also increases in patients with baseline renal impairment, concomitant statin use, and obesity.[12,13] Rhabdomyolysis usually occurred after a week of receiving daptomycin but has also been reported after receiving only two doses as well. The pathophysiology of daptomycin-related rhabdomyolysis has been attributed to its mechanism of action since it binds to the skeletal muscle cell membrane causing membrane disruption, leakage of CK from affected myofibers, and cell death.[14]

Rhabdomyolysis diagnosis

The diagnosis of rhabdomyolysis can be easily missed without clinical suspicion since symptoms of muscle injury are often nonspecific. Laboratory tests (Table 2) are required even though history and physical examination are suggestive.

Creatinine kinase

Creatinine kinase concentration, mainly the CK-MM subtype, is the most sensitive laboratory test for muscle injury. Serum CK begins to rise 2 to 12 hours after the onset of muscle injury, peaks within 24 to 72 hours, and declines at a constant rate of approximately 39% over 7 to 10 days (Figure 1).[15] Creatinine kinase has been reported to rise 7-10 days after the initiation of daptomycin.[21] A CK cut-off value of >1000 IU/L or >5 times the upper limit of normal (ULN) together with signs and symptoms suggesting myopathy can make the diagnosis of rhabdomyolysis.[16] The exception is statin-induced rhabdomyolysis which is defined by CK > 10 times ULN with muscle symptoms and renal impairment or a CK > 50 times UNL. Higher concentrations of CK indicate more muscle injury and a higher risk of kidney injury. The persistent elevation of CK suggests continuous muscle damage or the development of compartment syndrome.[17]

Serum and urine myoglobin

Myoglobin transports oxygen to the mitochondria of skeletal and heart muscle at a low partial pressure of oxygen. After muscle damage, the circulating myoglobin levels exceed the plasma protein binding capacity and are excreted in the urine. Myoglobinuria is a true

pathogenic factor in rhabdomyolysis associated with acute kidney injury. However, the half-life of urine myoglobin is only 2-3 hours, and myoglobinuria may not be detected. Serum myoglobin is the first enzyme that increases within 1-3 hours after muscle injury, peaks within 8-12 hours, and returns to normal within 24 hours after injury (Figure 1). Given the rapid drop in serum myoglobin and the short half-life of urine myoglobin, this test is not as sensitive as CK since increased levels may not be detected in every patient. Moreover, the urine dipstick used to detect myoglobinuria also reacts with the globin fragment of hemoglobin. Thus, in hemolysis patients, the specificity is very limited.[8,17]

Hyperuricemia

Hyperuricemia is an elevated serum uric acid level greater than 6.8 mg/dL that may predispose patients to form monosodium urate crystals.[19] With the formation of monosodium urate crystals, hyperuricemia may progress to acute gouty arthritis that typically involves the first metatarsophalangeal joint.[20] Predisposing conditions for gout depend on temperature and pH variations as well as the overproduction and underexcretion of uric acid.[19] At physiologic temperature and pH, monosodium urate crystals can form in the presence of hyperuricemia.[19] When temperature and pH are low, urate crystals can form in peripheral joints even if uric acid levels are below 6.8 mg/dL.[19] Although hepatic urate production by the purine degradation pathway is a cause of hyperuricemia, renal and gut underexcretion of urate tends to be a primary cause of hyperuricemia.[19] Hyperuricemia occurs in rhabdomyolysis due to the breakdown of muscle cell nucleic acids that release purines which are metabolized into uric acid in the liver. It can cause renal tubular obstruction due to the insolubility of uric acid. Our patient

developed hyperuricemia-induced gouty arthritis secondary to rhabdomyolysis which has never been reported. Renal impairment causing a decrease in renal urate excretion and a release of purine from muscle injury might be the factors leading to hyperuricemia-induced gouty arthritis secondary to rhabdomyolysis in this patient.

Others laboratory tests

Electrolyte abnormalities that occur as a consequence of muscle cell leakage include hyperkalemia, hyperphosphatemia, and high anion-gap metabolic acidosis. Hyperkalemia may also result from kidney injury and metabolic acidosis. High serum phosphate can bind to calcium causing the deposition of calcium-phosphate in soft tissue causing hypocalcemia. The increase of enzymes in muscle, including lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine dehydrogenase (ALT), and aldolase, can also occur but has low specificity since increased levels develop in many conditions. Serum creatinine can also be increased disproportionately to blood urea nitrogen due to the release of preformed creatine from damaged muscles.[8,17] Hypoalbuminemia occurs due to capillary damage causing the release of albumin into the extravascular space. Hyperkalemia is usually the first electrolyte abnormality and can be fatal. Thus, as soon as rhabdomyolysis is suspected, electrolyte and CK levels should be measured.[7] Muscle and kidney biopsies are not required to make this diagnosis.

Complications

Complications of rhabdomyolysis include acute kidney injury, arrhythmia caused by hyperkalemia or hypocalcemia, hypovolemia from the influx of fluid into necrotic muscle, compartment syndrome as a result of the ischemic and edematous muscle increasing intercompartmental pressure, and hepatic dysfunction due to a protease released from the injured muscle causing hepatic inflammation.[8]

Treatment

The goal of the treatment is to prevent or manage AKI and monitor complications. Early administration of intravenous fluid in patients who are not volume overloaded to maintain adequate renal perfusion and urine output is the most important intervention to prevent AKI and decrease renal toxicity effects from myoglobin. Nephrotoxic medication should also be discontinued. Recommendations on the type and rate of intravenous fluid are still controversial. Electrolyte abnormality should be treated and monitored closely. For hyperuricemia, allopurinol should be given orally at 300 mg if the uric acid level is more than 8 mg/dL or at least 25 present increases from baseline. There are no data supporting the use of rasburicase for the treatment of hyperuricemia-associated rhabdomyolysis. Hypocalcemia should be corrected only in severe and symptomatic hypocalcemia. Renal replacement therapy (RRT) should be started when indicated. However, the type of RRT still needs more study. The guideline suggests against routine use of loop diuretics, urine alkalinization with sodium bicarbonate, mannitol for the osmotic diuretic effect to prevent obstructive myoglobin casts, and antioxidants for prevention of rhabdomyolysis-induced kidney injury.[18] Whereas giving fluid is the most important treatment, fluid overloaded can also be harmful to the kidney. Thus,

maintaining a normal volume status is the best treatment strategy. For patients on daptomycin, monitoring CK levels during treatment to monitor muscle injury to reduce the risk of rhabdomyolysis is recommended. Co-administration of statin should also be avoided.

Our patient received a high dose of daptomycin (8mg/kg/day) for the treatment of septic arthritis. Symptoms of rhabdomyolysis developed after receiving intravenous daptomycin on day 4 when he presented with generalized weakness and muscle pain and was found to have AKI with elevated serum CK and myoglobin without myoglobinuria and RBC in the urine. Daptomycin was discontinued, and fluid was started on admission. He then developed hyperuricemia causing an acute gout attack on the fourth day of admission despite normal serum uric acid a week ago for which he was started on prednisone treatment. After receiving intravenous fluid, creatinine improved on the second day of admission and went down to his baseline creatinine on the third day of admission. The CK level also came down to below 5000 intl units/L on the fourth day of admission. Acute gouty arthritis symptoms significantly improved after the second day of prednisone treatment. Other laboratory results including AST, ALT, phosphorus, and uric acid levels, also decreased to normal levels in six days. No renal replacement therapy was required in our patient.

Early onset rhabdomyolysis might be explained by daptomycin dosing which was based on his actual body weight (ABW) (90 kilograms) with a total dose of around 700 mg daily; if the dose were calculated based on his ideal body weight (IBW), it would be around 400 mg daily based on an IBW of 50 kilograms in a patient with other risk factors, including concomitant statin use and predisposing chronic kidney disease stage 3A. Current Food and Drug

Administration (FDA)–approved daptomycin dose depends on ABW. Some studies compared the clinical outcomes of IBW versus ABW daptomycin dose showing no statistically significant difference in clinical success, microbiological outcomes, length of hospital stay, mortality, and adverse effects between both groups.[22] Other data studied clinical and safety outcomes in obese patients with a body mass index of $\geqslant$30 kg/m^2 comparing ABW daptomycin dose versus adjusted body weight (AdjBW) showing that both groups were statistically equivalent for clinical failure (i.e., development of resistance on subsequent cultures or recurrent signs or symptoms of infection requiring antibiotic adjustment) and 90-day mortality. There was no statistically significant difference between both groups regarding the combined safety endpoint (creatine phosphokinase elevation, patient-reported myopathy, and rhabdomyolysis).[23] Further research is required to determine a proper dosing method for daptomycin for different types of infections and organisms regardless of patients' weight to provide better clinical outcomes and an improved safety profile.

Conclusion

In conclusion, we report a rare case of a patient who developed symptoms of rhabdomyolysis while on daptomycin sooner than the typical 7-10 days after receiving daptomycin therapy. The case was further complicated by the development of acute gouty arthritis. We focused on fluid management and prednisone as the treatment for gout given his poor kidney functions. This case should encourage earlier and more frequent monitoring of creatine kinase levels in patients on daptomycin to proactively detect and prevent rhabdomyolysis and associated complications.

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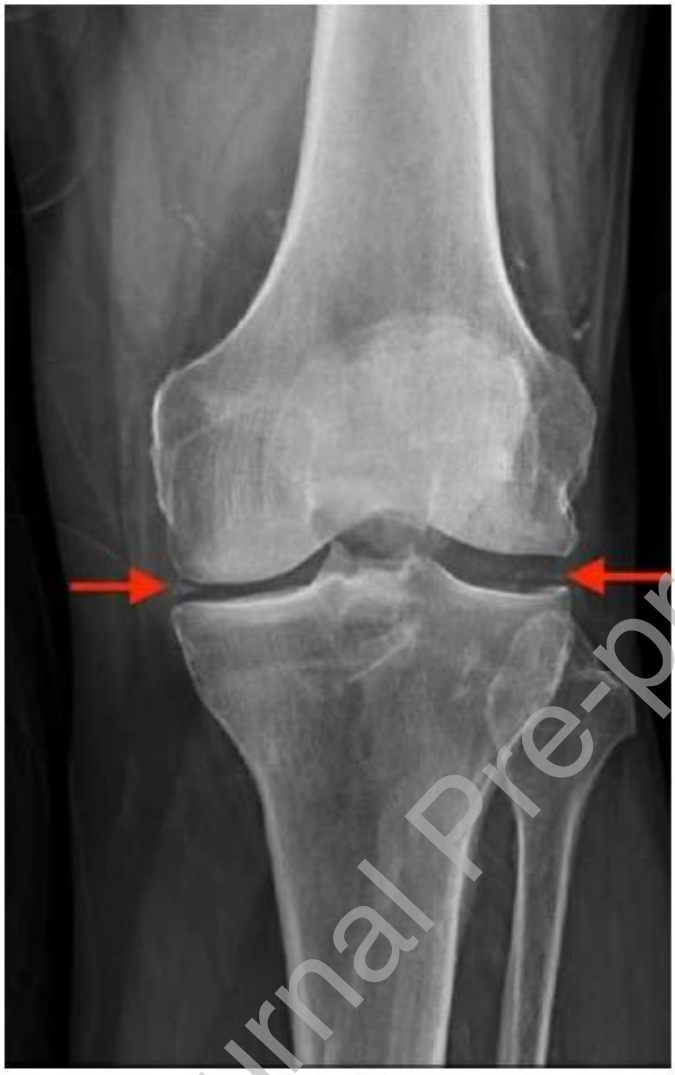

Figure 1: Creatinine levels from hospital day 1 through day 12

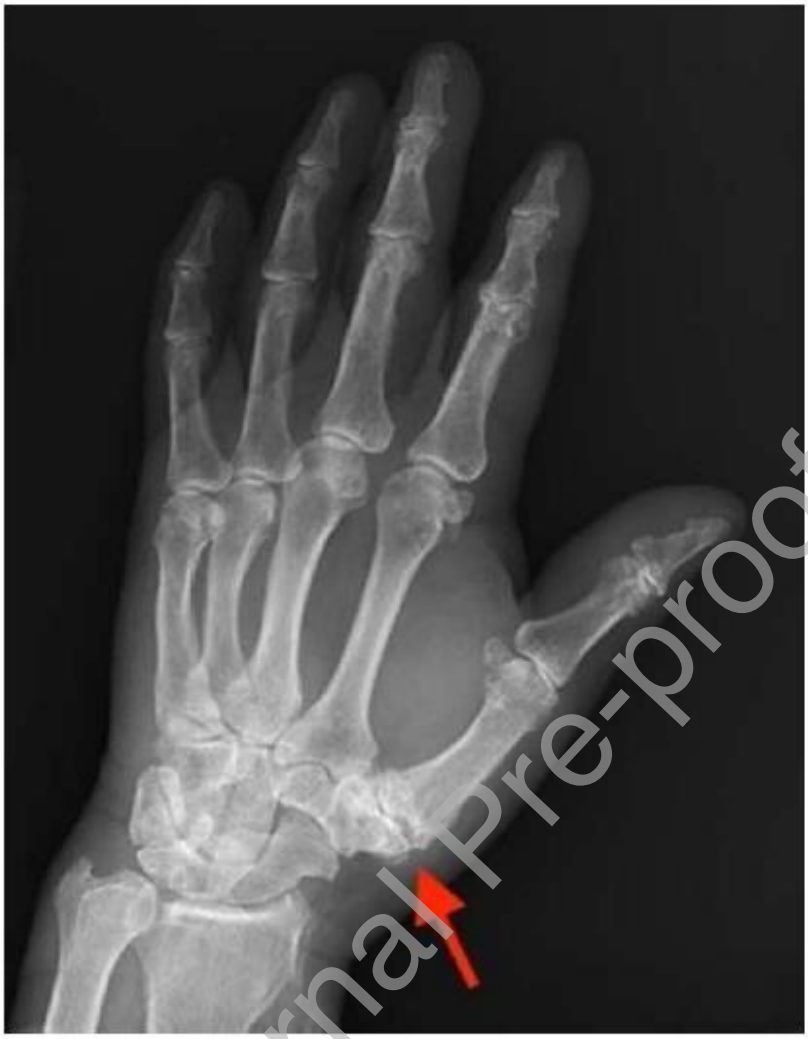

Figure 2: Creatine kinase levels from hospital day 1 through day 10

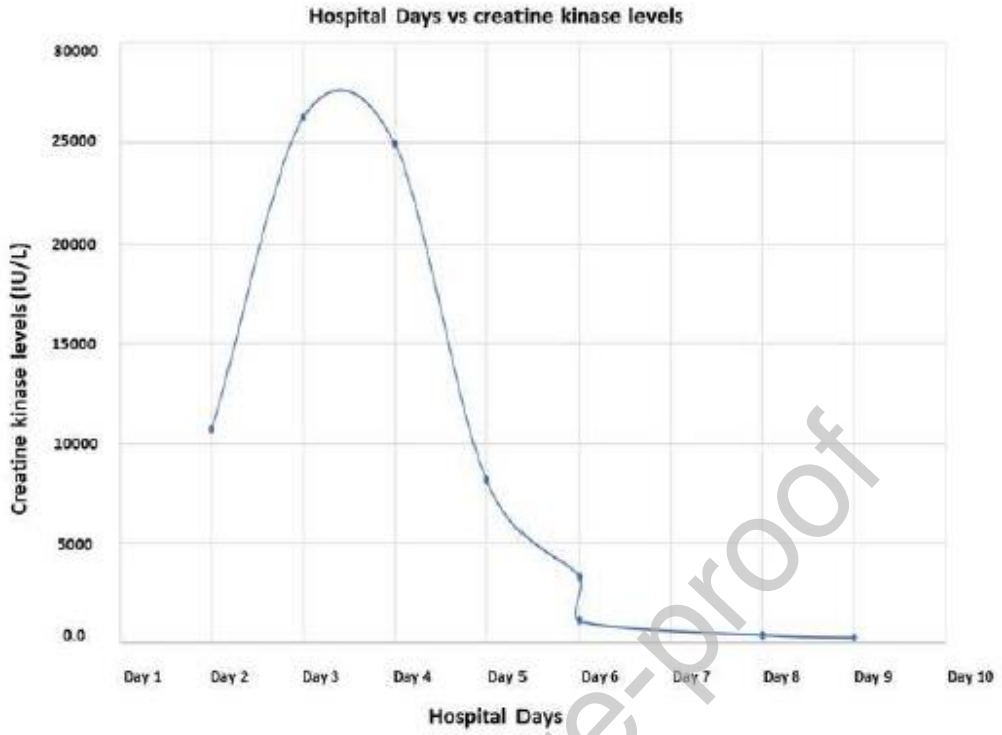

Figure 3: Left knee X-ray showing chondrocalcinosis of the medial and lateral compartments (red arrow).

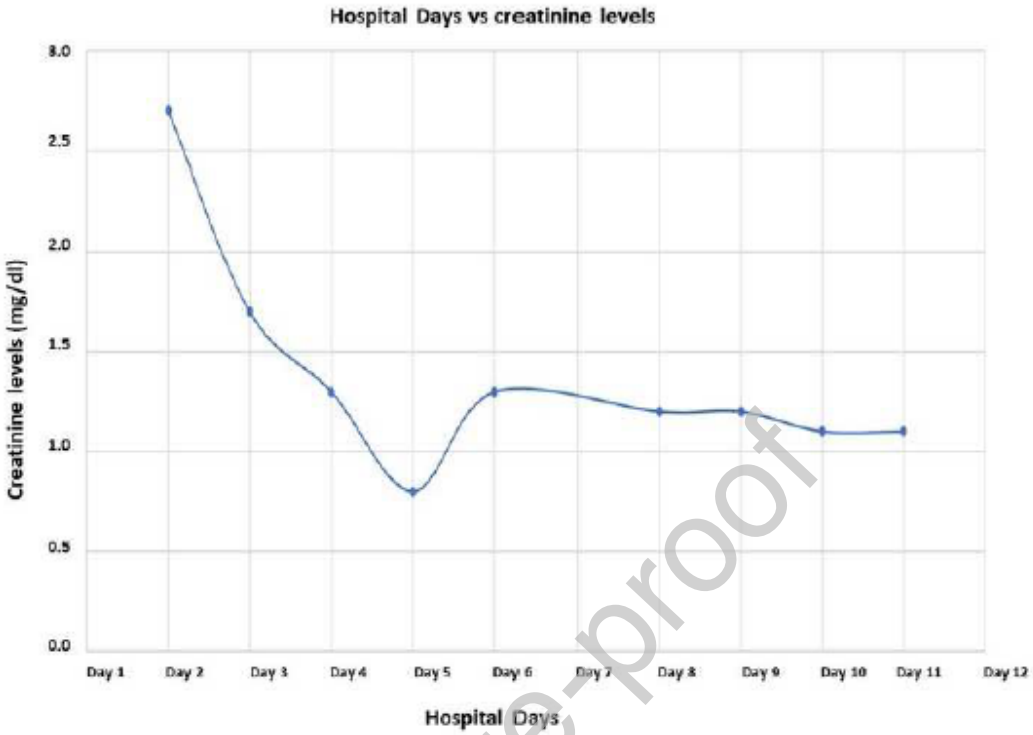

Figure 4: Left hand X-ray showing small periarticular erosions consistent with gout (red arrow).

Table 1: Causes of rhabdomyolysis

Congenital (Genetic)	
Carbohydrate metabolism disorders	Myophosphorylase, phosphofructokinases, phosphoglycerate kinase, lactate dehydrogenase
Lipid metabolism disorders	Acetyl-CoA dehydrogenase, carnitine palmitoyl transferase II

Mitochondrial disorders	Succinate dehydrogenase, coenzyme Q10, cytochrome c oxidase
Acquired	
Trauma	• Crush injuries • Electrical injuries • Vascular/orthopedic injuries
Strenuous exercises	
Prolonged immobilization/coma	
Body temperature-related muscle injury	• Heat stroke • Malignant hyperthermia • Neuroleptic malignant syndrome
Electrolyte abnormalities	Hypokalemia, hypophosphatemia, hypocalcemia
Infection	*Staphylococcus aureus, Streptococcus pyogenes, Clostridium* spp
Toxins	Heroin, cocaine, amphetamine, snake venom, mushroom
Drug-induced	Statins, fibrates, colchicine, protease inhibitors, and antimicrobials (antibiotics as macrolides (erythromycin, azithromycin), Bactrim, daptomycin, linezolid, cefaclor, cefditoren, meropenem, piperacillin-tazobactam and antifungals as amphotericin B)