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Rhabdomyolysis 2009

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Rhabdomyolysis (RML) is a clinical and biochemical syndrome with varied etiology where skeletal muscle fiber injury provokes the release of myocyte contents into the circulation. When RML occurs the clinical manifestations may range from asymptomatic elevations in creatine phosphokinase (CPK) to varying degrees of muscle weakness, tenderness, or pain. In complicated cases RML occurs with crush syndrome, acute renal failure (ARF), disseminated intravascular coagulation (DIC) and multiple organ failure. The outcome varies depending upon the precipitating cause, duration, severity of RML, and extent of renal failure.[1-9]

RML is caused by physical, chemical, or biological factors. Observed since biblical times, the Old Testament refers to a plague affecting the fleeing Israelites after consumption of quail called Coturnism. In the Mediterranean region, quails consume hemlock herbs, which contain coniine and results in human intoxication and RML following quail ingestion.[10,11]

The modern study of RML started with the seminal studies by Bywaters and Bell who described the crush injury victims during the 1940-1941 London *blitzkrieg* bombing raids of World War II.[12-14.] Since then, etiological factors including traumatic, nontraumatic, and genetic increased to more than 100.[1-9, 15]

This review will illustrate the RML spectrum with seven brief case reports followed by definition, signs, symptoms, diagnosis, pathophysiology, causes and risk factors, epidemiology, management and prognosis.

CASE REPORTS:

Case 1. *Nontraumatic Exertional RML*: A 19-year-old male inmate was admitted for evaluation of myalgias and hematuria. For the two days prior to admission, he was in his cubicle doing repetitive calisthenics (crunches) for more than one hour each day. Upon admission the CPK was 200,100 U/L (normal 21-232 U/L), AST 2845U/L (normal 15-37 U/L), ALT 356 U/L (normal 30-65 U/L), myoglobin 3,884 ng/mL (normal less than 50 ng/mL). The BUN was 10 mg/dL and creatinine 0.9 mg/dL. The physical exam was negative except for moderate swelling, tenderness, and tightness over the quadriceps muscles of both lower extremities. He was treated with the 800-100-100 regimen, as delineated in the management section below and under close daily biochemical and clinical monitoring, the creatinine remained normal. He had adequate urinary outputs and the CPK's gradually decreased to 49,222 U/L in four days and to 749 U/L in nine days (See table 1 for flow sheet of labs). He required no dialysis and was discharged in a stable condition after a prolonged discussion and counseling regarding unconditioned exercise.

TABLE 1

CHEM	NA	K	CL	CO2	GLUC	CA	PHOS	MG	BUN	CREAT
10/03/07 2140	138	4.2	102	26	99	8.9			10	0.9
10/05/07 0240	140	4.3	105	24	85	9.1	4.0		10	1.0
10/06/07 0335								2.0		
0338	142	4.0	106	20L	89	8.8			15	1.0
10/07/07 0600	141	3.6	106	26	95	8.9			16	1.0
10/08/07 0414	144	4.1	107	27	91	9.3			18	1.0
10/09/07 0316	141	4.0	108	25	80	8.9			17	1.0
10/10/07 0304	142	4.0	108	26	90	9.1	5.5H	1.8	15	1.1
10/11/07 0327	144	3.8	109H	25	87	9.0			17	1.0
10/12/07 0325	142	3.8	108	27	96	9.1			18	1.1
10/29/07 1835	142	3.9	105	26	93	9.1			10	1.0
1835							4.9	1.8		
10/30/07 1420	142	3.9	107	28	109H	8.8			9	0.9
11/01/07 0308	140	4.0	105	26	92	8.8			12	0.9
11/02/07 0238	144	4.4	107	28	89	9.5			10	0.9

CHEM	URIC A	ALB	GLOB	A/G RA	TP	CPK	AST	ALT	ALP	AMMONI
10/03/07 2140		4.3	3.2	1.3	7.5	(*)H	2845H	356H	109	
10/04/07 0510						(*)H				
10/05/07 0240	3.9	3.7	3.1	1.1	6.8	(*)H	2637H	415H	101	
10/06/07 0335						(*)H				
0335										43
0338		3.7	3.3	1.1	7.0		2499H	474H	109	
10/07/07 0600		3.6	3.0	1.2	6.6	49222H	1813H	452H	104	
10/08/07 0414		3.4	3.0	1.1	6.4		815H	363H	102	
10/09/07 0316		3.2	2.9	1.1	6.1	3866H	351H	271H	94	
10/10/07 0304	5.6	3.2	2.9	1.1	6.1	2020H	171H	214H	87	
10/11/07 0327		3.3	2.9	1.1	6.2	1234H	99H	177H	87	
10/12/07 0325		3.4	2.8	1.2	6.2	749H	66H	152H	85	

Other Tests	ANION GAP	CK-MB UNIT	CK-MB INDX	MYOGLOBIN	ABS NEUTRO	ABS NEUT M	CC
10/03/07 1855							
2140	10						
2140						11.2H	
10/05/07 0240	11						
0240					7.7H		
10/06/07 0335				3884.0C			
0338	16H						
10/07/07 0600	9			1242.2C			
1505							
10/08/07 0414	10			473.3C			
0414						5.9	
10/09/07 0316	8			294.3C			
10/10/07 0304	8			282.5C			
10/11/07 0327	10			198.9C			
10/12/07 0325					5.5		
0325	7						
10/29/07 1835	11						

CBC	WBC	RBC	HGB	HCT	MCV	MCH	MCHC	RDW	PLT CT
10/03/07 2140	14.3H	5.98H	18.3H	52.8H	88.4	30.7	34.7	11.6	229
10/05/07 0240	10.5H	5.49	17.1	49.2	89.6	31.2H	34.8	12.5	209
10/08/07 0414	8.5	5.25	16.4	47.0	89.4	31.1H	34.8	12.6	218
10/12/07 0325	8.4	5.14	16.1	45.9	89.2	31.3H	35.0	12.6	262
10/29/07 1835	11.6H	5.58	17.3	49.3	88.4	31.0	35.0	12.9	321
11/01/07 0308	9.2	5.25	16.4	46.9	89.3	31.3H	35.0	13.0	228

Case 2. *Alcohol Induced RML:* A 55-year-old female alcoholic with bipolar disorder admitted after a fall at home with minor trauma to the right side of her face and temple. At home she had been on treatment with quetiapine 300 mg/d, clonazepam 8 mg/d, temazepam 30 mg/d, tramadol 50 mg QID, carisoprodol 700 mg/d, hydrocodone/acetaminophen 10/325 mg QID. Upon admission the BUN was 41 mg/dl, creatinine 2.9 mg/dl, AST 1,369 U/L, ALT 373 U/L, myoglobin 39,120 ng/ml, CPK 56,057 U/L, aldolase was 106 U/L. The blood alcohol level was 190 mg/dl. The urinalysis showed 3 + occult blood and the microscopic exam showed no WBCs or RBCs. She had acute renal failure and the serum crea-

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tinine gradually rose to 8.1 mg/dl over three days. She required hemodialysis for two weeks and was later transferred to rehabilitation when her condition improved.

Case 3. *RML with compartment syndrome:* A 26-year-old male presented to an outlying rural hospital for evaluation of bilateral pain to lower extremities. A week prior to admission he was dancing for several hours and felt sudden pain in his lower extremities. Two days later he was dragging his legs in order to walk, so he saw a local doctor. He was treated symptomatically for shin splints, but due to deteriorating weakness he came to El Paso. Upon admission the CPK was 11,101 U/L, creatinine 1.1 mg/dl, AST 583 U/L, ALT 484 U/L, and myoglobin 640 ng/ml. On the initial evaluation he was noted to have compartment syndrome with bilateral foot drops that required immediate release and several daily debridements of necrotic muscles of lower extremities (Photo 1) by orthopedic and plastic surgeons. With treatment, the CPK gradually decreased to 1,335 U/L over five days but the creatinine remained unchanged. He later was transferred to a specialty rehabilitation hospital for antibiotic and hyperbaric oxygen therapy. He has since required the use of ankle foot orthosis braces and cane for subsequent ambulation.

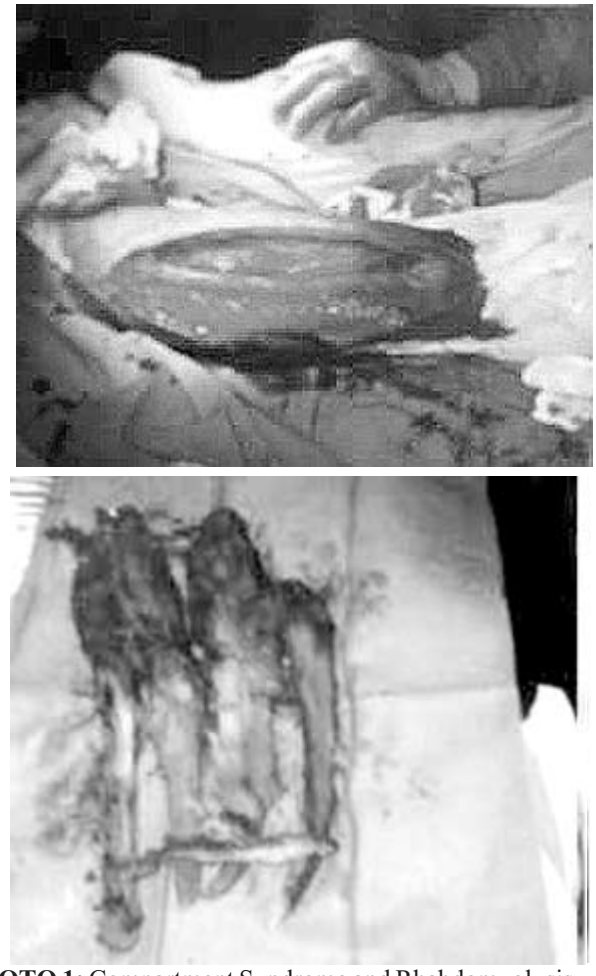

PHOTO 1: Compartment Syndrome and Rhabdomyolysis

Case 3 required immediate compartment release plus two separate surgical interventions. Despite attempts to salvage as much as possible, several muscles did not survive and required excision.

Case 4. *Seizure Induced RML:* A 25-year-old male with a 13 year history of seizures was admitted for status epilepticus and acute renal failure. Due to several days of nausea and vomiting the patient skipped his prescribed medications of carbamazepine 400 mg BID, lorazepam 2 mg qd, and phenobarbital 100 mg qd. He developed continuous seizure activity for more than an hour and fell sustaining loss of consciousness. Upon admission the BUN was 39 mg/dl, creatinine 3.8 mg/dl, CPK 8,460 U/L, and myoglobin 1,110 ng/ml. The urinalysis was 1+ for blood and the microscopic exam was negative for RBCs, WBCs, and nitrites. He was rehydrated and treated medically (see management below) without hemodialysis. The creatinine and CPK gradually decreased to normal levels in six days and he was discharged in an improved condition.

Case 5. *Exercise Induced RML:* A 23-year-old college female with an otherwise negative medical history was admitted for evaluation of pain to both lower extremities. Prior to admission she was cycling in the gym strenuously for an hour during her first visit. She took ibuprofen but pain persisted and she saw her internist who admitted her for evaluation of abnormal liver function tests AST 537 U/L, ALT 140 U/L, increased CPK 37,795 U/L and myoglobin 4,031 ng/ml. She was treated medically without dialysis as noted below. The CPK increased to 76,175 U/L the next day and gradually decreased to 2,870 U/L over the next six days under close biochemical and clinical observation. The serum creatinine remained normal throughout her hospital stay ranging from 0.7 to 0.8 mg/dl.

Case 6. *Crush Induced RML:* A 23-year-old male with history of drug abuse was admitted for oliguric renal failure and painful swelling of his left arm. He had injected himself with heroin, sled from his bed to the floor where he remained in a coma overnight, and he was lying on his left side until "found down" by his family. As a result of the self induced crush injury he developed a compartment syndrome which required a fasciotomy to improve muscle ischemia. After the fasciotomy the muscles bulged (Photo 2, reproduced from reference 14). He had a subsequent closure three days later and required hemodialysis for two and a half weeks. He lost the ability to move his left arm due to neural damage and ischemia. Weeks later, he became depressed and had a recurrent episode of heroin-overdose and was found dead at home.

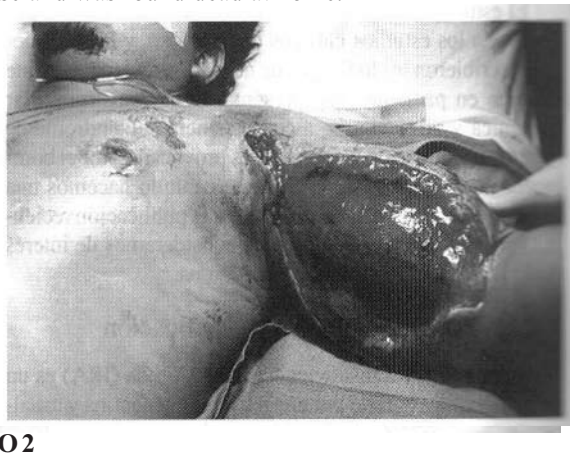

PHOTO 2

Case 7. *Medications induced RML: A* 42-year-old male with end stage renal disease secondary to diabetic nephropathy and hypertensive nephrosclerosis was admitted for evaluation of back and leg pain. A week prior to admission, he fell and was advised to

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come to the hospital but declined. He had been on peritoneal dialysis for approximately one year and was on treatment for hyperlipidemia with simvastatin 80 mg and gemfibrozil 600 mg qd. Upon initial evaluation the creatinine was 7.3 mg/dl and CPK was 10,173 U/L, and the CPK continued to increase to 26,054 U/L six days later. He was anuric and declined hemodialysis and the number of peritoneal cycles was increased. The CPKs gradually decreased to 8692 U/L by day ten and to 1466 U/L by the time of discharge on day 13. Moving parallel with the CPK, the myoglobin level upon admission was 27,217 ng/ml, peaked at 31,552 ng/ml six days later, lowered to 18,365 ng/ml by day ten, and decreased to 2,793 ng/ml by day thirteen.

Definition: The word Rhabdomyolysis is derived from Greek: *rhabdos,* which means rods*, myo,* refers to muscle, and *lysis* is breakdown. Thus RML is the breakdown of the muscle fiber myocytes which may be injured by a legion of etiological factors. When RML occurs the myocyte contents including myoglobin, potassium, and enzymes, are released into the extracellular compartment. Some of these may be harmful to the kidneys.[1-18]

Symptoms: Vary from mild in asymptomatic cases to severe. Fatigue may be present, myalgias, cramps, muscle stiffness, nausea, emesis, joint pains, local weakness of affected muscles to generalized muscle weakness, paralysis, fever, weight gain, confusion, agitation, seizures, delirium, shock and coma[1-15] as illustrated in the above vignettes.

Signs: Early detection requires a high index of suspicion. Upon examination the affected muscles may be tender and boggy or bruised. The overlying skin is reddened with local swelling and induration. The signs of the underlying disease or predisposing risk factors may be present. Anuria may be observed. Signs of multiple trauma or a crush injury may be present. RML may be less obvious in exertional RML, hypophosphatemia or viral infections. If a compartment syndrome has developed a foot drop or arm or wrist drop may occur as described below. Typically one of the initial signs of RML is discolored urine such as pink, tea, golden brown, red or cola-colored urine. Biochemical studies show that the MM isoform of CPK is very high, serum myoglobin and urine myoglobin may be increased as well. Serum creatinine, aldolase, potassium, LDH, AST, ALT, phosphorus, uric acid levels may be high.[1-17]

In certain disasters or earthquakes, muscles affected by crush injuries may exhibit ischemia or pressure necrosis of the skin. Dead muscle may cause a large amount of fluid to move from the blood into the muscle leading to shock, impaired renal blood flow, and associated consequences.[16,17] In more advanced stages of RML, shock signs may be present. The urinalysis may show myoglobin and/or dark brown pigmented casts of acute tubular necrosis in the sediment, as well as abnormalities in the urinary electrolytes, osmolalilty and other urinary indices of acute renal failure. Typically the urinalysis is positive for hemoglobin yet there are no RBCs in the microscopic exam.[1-9]

Diagnosis: RML should always be suspected in patients with a history or clinical exam consistent with muscle damage from trauma or ischemia. The hallmark of RML is elevated serum muscle enzymes. Serum myoglobin levels tend to rise early and are unpredictably eliminated by hepatic metabolism.[2] The urine benzidine dipstick, where the reagent reacts with myoglobin, hemoglobin and red blood cells, may be positive for blood but on urine microscopy no RBCs are usually seen. Myoglobin causes discoloration of the urine but not of the plasma. Urine myoglobin tests are not very reliable and not recommended. The most reliable diagnostic test is the level of CPK or CK in the blood.[2-4,9] RML is usually defined as an increase of five to ten times the upper limit of normal[7,8] which ranges from 21 to 232 U/L. About 94% of the CPK in skeletal muscle is the CPK MM isoform and the CPK MB accounts for 6 % or less.[9] The CPK has a half-life of 48 hours. The CPK levels tend to rise during the initial 12 hours after damage, remain elevated for one to three days, and then fall gradually unless the patient has end stage renal disease (Case 7), has ongoing muscle damage, or has a compartment syndrome. A *second wave phenomenon* has been described, after the initial injury CPK levels raise again when contiguous muscle masses release additional muscle enzymes from damaged myocytes. [1-9,15-17] This phenomenon is mediated by calcium[18,19]

Several *subtypes of CPK* exist: The CPK-MM isoform is found in striated muscle, the CPK-MB isoform in cardiac muscle and CPK-BB isoform in brain, blood vessels, bowel and some neoplasms. A small percentage of MB fraction is found in skeletal muscle. During RML extreme quantities of CPK-MM may be released with peak concentrations at 100,000 U/L or more are not unusual (see Case 1). CPK levels can remain elevated much longer and in a more consistent manner than myoglobin. Therefore CPK-MM is more reliable than myoglobin in assessing the presence and extent of muscle damage. The initial and peak CPK levels may have a linear relationship with subsequent risk of developing acute renal failure. The triad of muscle weakness, myalgias, and dark urine may be present in about 50% of adults but is not as frequent in children.[1-9]

Anyone who just completed strenuous exercise, especially in deconditioned subjects under hot or humid conditions, may develop RML.[15] It may also be detected after a recent surgery, locally invasive pyomyositis, or if the individual has a chronic muscle disorder. In the case of chronic muscle disorder, the patient may have a CPK of several hundred U/L but in RML the CPK may be elevated from thousands to millions U/L and is mostly represented by the CPK-MM isoform. RML should also be suspected in alcoholics, drug abusers, and anyone who may have sustained trauma, prolonged immobilization, muscle compression, crush injury, extreme temperatures, electrical injury, arterial or venous thrombosis, vasculitides, embolism, or clamping of major blood vessels.[1-9]

Compartment syndrome

Somatic muscles comprise 40-50% of the body mass. Most striated muscles are surrounded by fasciae, ligaments, bones and other structures. The intramuscular pressure is usually around 0-10 mm Hg. Compartment syndrome occurs when there is increased pressure in a closed anatomic space provoked by the compression of swollen, injured muscles which may affect the viability of the neuromuscular tissues within the compartment. When muscles are injured, the transcellular pump systems fail and the myocytes burst their components into the extracellular space, drawing additional water into a restricted compartment. The muscles swell after imbibing elements from the extracellular compartment and pressures build within the fascial muscular compartment. Once the compartmental pressures surpass the intramuscular artery, arteriole and venous pressures the blood flow decreases, the oxygenation of tissues within a given compartment decreases and they are at risk for necrosis. Neural tissue has approximately 6 hours prior to develop-

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ment of permanent injury, whereas muscular tissue has approximately 8 hours of hypoxic time prior to necrosis. Cellular hypoxia ensues as blood flow decreases, and tissues subsequently become necrotic. When the blood supply decreases there is decreased sensation and pain in the affected area. This can also develop after fluid resuscitation and is a cause and complication of RML.[19-21] This may be verified by measuring the pressure in a fascial compartment, where values of *30-50 mmHg or 4-6.5 kPa indicate a severe compartment syndrome* and the need of fasciotomy to relieve increased pressure, preserve muscle and organ function, and avoid paralytic damage to the peripheral nerves.[2-5,12-21]There are 7 P's which may help in the diagnosis of a compartment syndrome (Table 2)

TABLE 2: 7 P'S OF COMPARTMENT SYNDROME
Pain on passive range of motion
Position of flexion may relax intramuscular fascia
Poikilothermia
Pallor of the extremity
Paresthesias: signs of ongoing neural damage
Pulselessness: late sign, lost vascularization
Paralysis: late sign, poor outcome (e.g. wrist drop or foot drop)

Causes: Anything that destroys somatic muscle tissue can provoke RML and this may occur as a result of traumatic, non-traumatic or genetic etiologic factors. Traumatic causes may include compression of muscles which occurs with a crush syndrome, obstruction of blood supply, or excessive muscle strain. The non-traumatic causes (see below) are five times more frequent than the traumatic. In the series by Gabow et al 59% had a history of multiple associated conditions.[1] Genetic factors account for about 10% of cases[5,7]. Familial myopathies should be suspected in patients with recurrent episodes of RML and the absence of other etiologic causes. Detailed lists of possible causes of RML are provided in major references[1-9]

The most frequent Risks Factors for RML may be easily remembered with this simple mnemonic: **I SPOT CASH (Table 3)**

TABLE 3: RML RISK FACTORS
I schemia or necrosis of muscles
S evere exertion (calisthenics, marathon runners,etc)
P oor physical condition
O verdose of drugs (cocaine, heroin, PCP, amphetamines, statins)
T rauma
C rush injuries
A lcoholism
S eizures
H eat Stroke & Intolerance

Common causes of RML: The most common cause of RML in the general population is physical exertion.[9] RML can be provoked by direct muscle injury after natural or man-made disasters, especially shock states, motor vehicle accidents, farm and industrial accidents, prolonged seizures, temperature extremes, hyperactivity, marked or excessive physical exertion. Excessive physical exertion leading to RML has been noted with violent calisthenics, weightlifting, marathon running; RML has been also noted during training of police cadets, military recruits and even in mechanical bull riders, bongo players and computer keyboard users. Boxing and karate may provoke RML. Victims of assaults, torture or child abuse may also show signs of RML.[1-9]

In the hospital setting: The most common cause of RML in hospitalized patients is drugs (ethanol, cocaine, heroin, amphetamines, ecstasy, phencyclidine, etc).[9] RML may occur after prolonged sympathetic stimulation (thyroid storm and phreochromocytoma), prolonged cardioversion and chest compressions, shock and septic states and a diversity of infectious agents. RML may also occur with tight dressing, casts, prolonged immobilization, carbon monoxide poisoning, hyperemesis gravidarum, malignant hyperthermia (idiopathic reaction to halothane), neuroleptic malignant syndrome (triggered by haloperidol and chlorpromazine), delirium tremens, status asthmaticus and epilepticus, diabetic ketoacidosis, chronic hypokalemia, hypomagnesemia and hypophosphatemia. RML has been reported after lightning, electrical injuries, deep burns, animal and insect bites, toxins and venoms. [1-9]

A long list of *pharmaceutical agents* can provoke RML including psychotropic agents, anesthetics, benzodiazepines, corticosteroids, narcotic analgesics, lipid lowering agents, antibiotics, paralytics, immunosuppressants, myotoxins, salicylates, antidepressants and antipsychotic agents. Therapy with statins may be associated with RML[22] and the risk is increased by concomitant therapy with cyclosporine, fibrates danazol or erythromycin. When statins are prescribed the risk is 0.44 cases per 10,000 patients annually but increases to 5.98 if a fibrate is added[22] (See Case 7). However other studies detected no increased risk.[23] Certain patients may have an idiopathic or hereditary or acquired condition with underlying disorders of the mitochondria, carbohydrate and lipid metabolism.[1-9]

Pathophysiology: The important underlying mechanisms in RML include muscle hypoxia, cell membrane injury with disruption of the sarcolemma, ATP depletion, and alteration of the sodium-potassium and sodium-calcium pumps with ensuing electrolyte abnormalities and organ dysfunction. The final common pathway of RML may be a disturbance in myocyte calcium homeostasis.[1-9, 18,19]

Damaged myocytes leak myoglobin, organic acids, phosphates, purines, thromboplastin, tissue plasminogen and other enzymes such as aldolase, LDH, AST and ALT. The latter two transaminases increase in about 25% of cases of RML and may be confused with acute liver injury in the early stages.[1,24] Gamma glutamyl transferases do not increase as result of RML and are useful to exclude hepatic injury. There is no troponin I in skeletal muscle.[9] Cardiac troponin levels may be increased in about half of all RML cases. Of these 58% were true positive (based on EKG and echocardiogram) 33% were false positives and 9% were indeterminate[25]

The changes in the clot promoting agents and thrombolytic substances that can occur during RML may predispose to disseminated intravascular coagulation.

Epidemiology: RML is a relatively rare disorder**.** Nichols and Koro estimated RML to be about 2 cases per 10,000 person-years. [23] and Sauret and associates reported 26,000 cases per year in the US.[26] Approximately 15-20 % of cases of RML will develop acute renal failure[2-9,26] In the Armenian earthquake in 1988, more than 1000 cases were noted and about one-third required dialyses.[27-29] Later in the 1990s after the Izmit earthquake in Turkey 462 patients received dialysis and were assisted by the International Society of

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Nephrology Renal Disaster Relief Task Force.[30]

Management: There is not a particular treatment suitable for everyone with RML and the treatment has to be tailored to each individual case and potential risk factors and complications. The management of RML primarily consists of correction of fluid, electrolyte, and renal abnormalities. Early detection and removal of any precipitating cause is of paramount importance as well as the early and aggressive management of patients with a crush syndrome and hypovolemic shock. Severe cases of RML should be managed in critical care units

A simple approach to RML consists of following: **ABCDEFGHI.** After the initial **ABC** (**A**irway, **B**reathing and **C**irculation) is addressed, the patient has to be closely observed in a monitored bed with serial measurements of K, P, Ca and Cr until the RML resolves. Then continue with **DEFGHI**:

Daily observations, daily weights, vital signs, strict intake and output.
Extracellular volume replacement and expansion
Forced alkaline diuresis, as noted below
Goal: maintain adequate organ perfusion, treat shock and preserve renal function
Hyperkalemia therapy as required
Individualize therapy depending on circumstances and clinical response.

Restoration of intravascular volume is of paramount importance and *induction of an alkaline solute diuresis* should be tried. No real consensus exists on volume, amount or timing. Cardiac and renal disease may limit the amount and rate of IV fluids to be used. In the acute phase of adult patients, initially 500 to 1,000 ml/hr of normal saline may be needed and preferably should be monitored with a central line. Most patients should have a Foley catheter, unless they are anuric. The ideal situation is to maintain an hourly urinary output of 150 to 300 ml. Caution should be taken to avoid volume overload and pulmonary edema. Depending on the clinical condition, the IV fluids may be changed to 5% dextrose or ¼ or 1/3 or 1/2 normal saline with 1 or 2 ampoules of sodium bicarbonate. To maintain urine alkalinized to a pH of 6 or higher, acetazolamide 250 mg may be added IV or per os. The only drawback of bicarbonate solutions is the decrease of serum ionized calcium.[2-7]

To *maintain adequate diuresis* a test dose of mannitol 12.5 gm IV BID can be given or added to the IVF provided the patient is not anuric or fluid overloaded. An alternate option is the *800-100-100 regimen* which is infused at 250 ml/hr over 4 hrs and titrated or modified according to the clinical condition, hemodynamics, urinary output and electrolytes. It consists of 800 ml of 5% dextrose, sodium bicarbonate 100 ml (two 50 ml ampoules of sodium bicarbonate) and 100 ml of 25% mannitol (two 50 ml vials of 25% mannitol). Mannitol is an osmotic agent that increases blood flow and glomerular filtration rate, scavenges free radicals and prevents obstructive myoglobin casts and a pigment nephropathy.[2-4, 10-12,14] Some studies report no apparent benefits to the alkaline mannitol diuresis[31] and as noted earlier the treatment has to be adjusted or discontinued depending on the clinical response and evolution. A *consulting nephrologist* should take care of any fluid, electrolyte or renal disorders and can start renal replacement therapies on a timely basis, if needed.

Necrosis of muscles and reperfusion injury may occur in patients with a crush syndrome after the blood flow into damaged tissue is restored and leads to the release of large amounts of toxic sarcoplasmic intracellular contents into the circulation, migration of leukocytes and production of free radicals and accumulation of up to 10 liters of fluid in affected limbs.[2,4-8,12-19,27-30]

Maintaining a high urine volume and alkaline urine pH (6 or higher) is highly desirable to prevent dissociation of myoglobin into its nephrotoxic components though sometimes this is not feasible.[2-4,8,12-14] A flow sheet of important clinical and laboratory parameters should be maintained (See Table 1, from Case 1). Close monitoring and treatment of potential complications are required and appropriate consultations should be requested as needed. When RML patients are in renal failure the medicines need to be adjusted according to prevailing renal function and the usual renal supportive and/or dialytic care is recommended until there is recovery of ARF.[14,26-29]

If hypotension, hypovolemia or shock is present, appropriate measures should be taken immediately even at the disaster area and later at the intensive care unit or telemetry unit. It is very important to start intravenous fluids before extrication in crush syndrome patients. Extrication of entrapped patients and rapid transport to a hospital setting is required as well as monitoring of compartment pressures in injured extremities.[2,4,16,19] The early complications of RML are metabolic and occur in the first 12 hours and include: hyperkalemia, hypocalcemia, hepatic inflammation, cardiac arrhythmias and arrest. Late complications occur thereafter and include reperfusion injury, compartment syndrome, DIC, and acute renal failure.[2-7,10-15]

Depending on the extent, duration and severity of the RML continuous electrocardiographic monitoring is advisable or mandatory to check for potential signs of hyperkalemia and cardiac arrhythmias. Potential cardiotoxicity may occur in hypocalcemic patients with potassium levels more than 6 mEq/l. A test dose of calcium gluconate or chloride will reverse these changes and hemodialysis may be required.

Hyperkalemia and metabolic acidosis or renal failure need to be monitored and treated accordingly. In general terms, hyperkalemia can be treated with calcium salts, intravenous sodium bicarbonate, hourly dextrose 50% 50 ml with 5 units of regular insulin; oral or rectal sodium polystyrene sulfonate (Kayexalate®). Life threatening abnormalities need to be addressed promptly. In certain cases, the initiation of acute hemodialysis may be required when the patient is very catabolic, hyperkalemic, acidotic, fluid overloaded or uremic and this may be required even on a daily basis.[2-4,14]

Hypocalcemia is commonly noted in the initial phase of RML. Usually, it does not require correction (it may increase intramuscular calcium deposition) but calcium infusion may be lifesaving for temporary reversal of hyperkalemic cardiotoxicity while preparing a patient for dialysis or for impending tetany or seizures. *Hypercalcemia* may occur during the diuretic phase of acute renal failure and is seen in patients that have received calcium in the early phases of RML.[2-12]

Usually the *CPK and potassium levels tend to peak 12 to 36 hours after* the initial insult and then gradually decrease over the next

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several days to weeks. Myoglobin detection may vary depending on prevailing residual renal function. All of these parameters may have a prolonged half life or can be eliminated slowly if there is no residual renal function or if additional muscular masses are affected.[2-9] A *second wave phenomenon* has been described wherein contiguous muscles may be damaged or if the patient is anuric after the initial episode (see progress of CPK in case 7).

Patients with severe extremity trauma (see table 2) should have compartment pressures measured especially in those at risk of a *compartment syndrome*, wherein an orthopedic consult is also required.

DIC should be treated with fresh frozen plasma and cryoprecipitate. Platelet transfusion is not helpful because of ongoing platelet consumption and endothelial cell activation which is a major component of cellular injury in RML.[9,32]

If the RML is not severe and if patient is hemodynamically stable, asymptomatic and in not acute distress, especially in recurrent cases, it can be managed in a regular floor or as outpatient under very close observation.

Prognosis: The prognosis depends on the precipitating cause. The overall survival rate after RML is about 77% and most deaths are usually related to other associated comorbidities.[2-9,12,14.16-20,26-30] RML patients who develop acute renal failure may have a mortality of 20%. An early detection, removal of precipitating risk factors followed by appropriate treatment, which may include vigorous volume replacement, urinary alkalinization, aggressive diuresis and/or hemodialysis, have improved significantly the outcome of patients with RML.[1-31]

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** For readers interested in additional RML references, it can be obtained via Google and the internet. A recent search yielded more than 927,000 potential links.

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