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Exogenous Causes of Myoglobinuria

- Review of 26 Cases -

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In this article, I review various causes of exogenous myoglobinuria(MU) and its pathogenesis in 26 consecutive patients admitted to emergency room, Asan Medical Center and determine whether there is a relationship between concentration of urine myoglobin(Mb) and acute renal failure(ARF) as a complication of MU. Serum and urine Mb were measured by RIA using myoglobin kit(Daiichi, Inc., Tokyo, Japan). The most common disorder of MU was septic shock with hypotension, followed by crush syndrome, major arterial occlusion by thormbosis, alcohol intoxication with status epilepticus, intoxication of unidentified snake venom and drug ingestion. On the basis of this limited amount of data, there is a significant association between high concentration in urine Mb(>300 ng/ml) and ARF(Fisher's exact test, $p<0.005$). To minimize the chances of development of ARF, routine urine Mb levels should be checked on patients at risk, especially septic shock with hypotension.

Key Words : *Myoglobinuria, Acute renal failure*

INTRODUCTION

It has been known that Mb is a major protein of the sarcoplasm with its critical function as an oxygen carrier. But massive MU can produce life-threatening complications(Better, 1989 ; Curry et al, 1989). Overt MU has been arousing curiosity to the physician, and management of ensuing ARF, challenging. Even more important are the varied causes of MU, which give clues as to the types and extent of injuries producing muscle necrosis. Acute muscle necrosis with MU include inherited disorders of muscle metabolism and other genetic diseases (Penn,1994). Exogenous causes include infections, crush syndrome(Majed O, 1991), drug and myotoxic agents, electrolyte imbalance, and extremes of ambient temperature with hypothermia or fever. The number of analyzed exogenous causes associated with MU and/or ARF has increased in the past two years in Asan Medical Center(AMC).

In this article, I review various causes of exogenous MU and its pathogenesis in 26 consecutive patients and determine whether there is a relationship between concentration of urine Mb and ARF.

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MATERIALS AND METHODS

The study was retrospectively made on 26 patients (22 men and 4 women between 26 and 71 years of age) admitted to the emergency room, AMC, between October 1, 1992, and December 31, 1994. Serum and urine Mb was performed by RIA measurement(Stone, 1975)(Rosano, 1977) using Mb kit(Daiichi, Inc., Tokyo, Japan). The test was done twice for the accurate determination. Serum CK, blood urea nitrogen, and creatinine were also measured. The oliguric ARF was defined with a daily increase in the serum creatinine level

greater than 0.5 mg per deciliter and with a rate of urine flow less than 400 ml per day, despite adequate fluid replacement(Grantham, 1988).

RESULTS

The most common disorders were septic shock syndrome(6 patients), followed by crush syndrome(3 patients), intoxication of unidentified snake venom(2 patients), alcohol intoxication with other combined disorders such as polymyositis and status epilepticus(3 patients), drug ingestion(1 patient) and other causes(only 1 patient, each)(Table 1). There was a predominance of men(male/female ratio, 5.5:1). Ten patients had more than two causes. The concentration of serum CK, urine and serum Mb is described in table 1. Raised serum CK(mean, 17732 units/L ; mean standard error(MSE), 4423 units/L in 24 patients) and Mb levels(mean, 2419 ng/ml ; MSE, 1394 ng/ml) were noted in all 26 patients with MU(mean, 1489 ng/ml ; MSE, 987 ng/ml). There was a tendency to develop ARF when urine Mb concentration is higher than 300 ng/ml(Fishers exact test, $p<0.005$).

DISCUSSION

Mb is found in skeletal and cardiac muscles of vertebrates. It has no measurable direct effect on respiration or ATP production by isolated skeletal muscle mitochondria but was shown to enhance the flux of oxygen across an oxygen gas-liquid interface when mitochondria were present(Cole et al., 1982). MU is an external manifestation of focal or diffuse muscle necrosis("rhabdomyolysis") that is severe enough for pigment escaping from muscle to be visible in the urine. Exogenous causes, such as infections, crush injury, drug and myotoxic agents, and electrolyte imbalance, attack MU more frequently than endogenous causes, which include inherited disorders of muscle metabolism and other genetic diseases(Penn, 1994). In exogenous causes of MU, I found that the most common disorders were septic shock syndrome, followed by crush syndrome, major arterial occlusion by thrombosis, alcohol and drug intoxication, and impaired muscle metabolism

Table 1. Clinical and laboratory features of patients with myoglobinuria

Patient	Sex	CK[1] (units/L)	Serum Mb[2] (ng/ml)	Urine Mb (ng/ml)	Oliguric ARF[3]	Cause of Myoglobinuria
1	M	1716	205.8	20.7	No	Snake bite
2	F	NT[4]	300	91.9	No	Toxic shock syndrome
3	M	1500	251.6	47.8	No	Thrombosis of major artery
4	M	1136	300	297.3	No	Alcohol intoxication
5	M	45712	7300	35	No	Crush syndrome with compression neuropathy
6	M	3928	300	38.9	No	Heat stroke
7	M	12040	300	87.4	No	MI[5] with cardiogenic shock
8	M	538	300	104.7	No	Thrombosis of major artery
9	F	3281	300	303	No	Hypokalemia
10	M	1440	300	30	No	Thrombosis of major artery
11	M	48356	300	174	No	Sepsis, acute respiratory failure
12	M	5158	300	300	No	Septic shock with hypotension, rhabdomyolysis, compression neuropathy
13	M	1217	800	300	No	Fever with sepsis
14	M	78002	300	300	No	Neuroleptic malignant syndrome, encephalitis
15	M	8251	300	300	No	Multipe trauma
16	M	24469	942	25568	No	Hepatic coma with seizure, diuretic-induced hypokalemia
17	M	13233	300	4874	No	Multiple trauma, coma
18	M	20000	300	300	Yes	Status epilepticus, alcoholics
19	M	5000	300	300	Yes	Fever, SLE[6], hypotension
20	M	13822	300	300	Yes	Polymyositis, hypotension, azotemia, alcohol drinking
21	M	46373	300	300	Yes	Frostbite with coma
22	M	48356	300	300	Yes	Pulmonary embolism, azotemia, rhabdomyolysis, CIP[7]
23	F	23252	34386	3464	Yes	Snake bite, DIC[8], altered mentality
24	M	NT	300	300	Yes	Sepsis with fever, pulmonary embolism, hypotension
25	M	874	300	300	Yes	Drowning with coma, muscle injury
26	F	58470	13296	300	Yes	Drug ingestion, rhabdomyolysis

CK[1] ; creatine phosphokinase. Mb[2] ; myoglobin. ARF[3] ; acute renal failure. NT[4]; not tested. MI[5] ; myocardiac infarction. SLE[6] ; systemic lupus erythematosus. CIP[7] ; critical illness polyneuropathy. DIC[8] ; disseminated intravascular coagulation.

of toxins.

Septicemia and MU include single reports of *Shigella, Salmonella blockley, and Escherichia coli*(Bowden et al., 1956 ; Rowland and Penn, 1972; Hendrick et al., 1980). There has been also one report of an elderly man with chills, myalgia, high CK, and MU who was shown to have Legionnair's disease(Posner et al., 1980). Severely involved muscles with massive necrosis and MU is the hallmark of a gangrenous limb infected with *Clostrium perfringens* and occasionally with *Clostrium septicum* gas gangrene(Weinstein and Barza., 1973). We have found in five patients(case 2, 11, 12, 13, 24) that MU was caused by extracellular bacterial infection with septicemia. But in one patient of systemic lupus erythematosus(case 19), the bacteria was not identified. The pathogenesis of MU in these septic shock syndrome caused by bacteria is related either to excessive endogenous heat, or to the effect of bacterial toxins or hypotension. Extreme body temperatures, which developed in some patients with typhoid fever or after administration of vaccine, resulted in MU(Penn, 1980).

The crush syndrome, or traumatic rhabdomyolysis, is the consequence of prolonged continuous pressure on the limbs(Majed, 1991). The development of severe extensive muscle necrosis from crush syndrome and the consequent MU, ARF and skin and nerve ischemia has been well known in comatose patients either of traffic accidents, or of building collapse due to earthquake (Better and Stein, 1990). A similar, less dramatic crush syndrome occurs in comatose patients who are immobile and narcotized for over 12 h with compression of dependent limbs or torso by their own heavy bodies(Penn and Rowland, 1972 ; Gordon and Newman, 1953). Three patients(case 5, 15, 17) with crush syndrome in this study were found in a comatose state. One of them(case 5), who ate raw oyster and drunk lots of alcohol, were found in a comatose state with the peroneal and radial compression neuropathy and skin bullae in dependent portion. Skin biopsy of bulla and blood culture and smear were unremarkable. Serum carboxyhemoglobin was not increased. So he was diagnosed as compartment syndrome, reinforced by high uptake of radionucleotide scanning with Technesium diphosphonate and conduction block of radial and peroneal nerves on dependent portion of arm and leg. The compression neuropathies of the nerves by the immobile body against bony prominences, which was painful and slow to resolve has been reported(Penn et al, 1972 ; Akmal and Massary, 1983). Although skin bullae and ulcerations have been atributed by some to a toxic effect of compounds such as barbiturates(Akmal and Massary, 1983), other studies also support a contribution from direct ischemic damage to skin(Schreiber et al, 1972). Another two patients had crush syndrome caused by multiple injury without compartment syndrome as a cause of MU.

Three patients(case 3, 8, 10) had major arterial occlusions(ileofemoral artery, femoro-peroneo-tibial and axillary artery, femoral and descending inferior myocardial artery, respectively) from thrombi. None of these patients had ARF, but Mb was detected up to 104.7 ng/ml. These MU due to infarction of muscle by arterial occlusion from emboli or thrombi had been reported (Bywaters and Stead, 1945; Adieshiah et al., 1992).

Alcohol-induced MU was first described in a series of reports by Fahlgren and colleages(Fahlgren et al, 1957). Three patients(case 4, 18, 20)are all chronic alcoholics in this study. The first patient was a heavy drinker with delirium tremens, but without ARF. The second had status epilepticus and ARF. The third had heavy binge drinking with severe hypotension, polymyositis and ARF. The histopathologic finidngs were dilatation of the sarcoplasmic reticulum(SR), loss of myofilaments, enlarged mitochondria with disorganized christae and increased numbers of lipid droplets (Urbano-Marquez et al, 1989). But the pathogenesis of MU caused by alcohol intoxication was not confirmed. Alcohol or its metabolite, aldehyde, may be directly toxic to muscle, interfere with muscle metabolism, or potentiate the toxicity of other drugs used simultaneously. Other postulated mechanisms include acute hypokalemia, and inhibition of cation transport with altered resting membrane permeability(Martin et al., 1971 ; Haller and Drachman, 1980). The drugs and toxins often exert their effect by familiar mechanisms such as coma with crush syndrome, excessive muscular exercise, fever, hypokalemia or some combination. Some compounds appear to be directly toxic to muscle membranes. One of our patients(case 26) ingested a small amount of methylalcohol unexpectedly. She had oliguric ARF with high CK and serum- and urine- Mb. Her kidney function was normalized after 2 months. Pathogenesis of her severe MU might be directly toxic effect on muscle membrane.

Most venomous snakes contain specific myotoxins in their venom. A 42-amino acid basic 3-polypeptide unit has been isolated from rattle snake venom which proved to cause MU in mice without concomitant paralysis(Fox et al., 1979). Two patients were bitten by an unidentified venomous snake. The vast majority of poisonous snake bites are inflicted by members of the

Crotalidae(pit viper) family in the United states(Ellenhorn et al., 1991). In Korea, only 2 species of snakes are venomous : Agkistrodon blomhoffii and Rhabdophis tigrina. The former is particularly well-known for snake venom toxicity. Moderate MU without ARF was found in one patient(case 1), but severe MU, ARF and disseminated intravascular coagulation caused the victum(case 23) dead. These venom probably contain myotoxin and direct toxic damage to muscle membranes. Ownby et al reported that the histopathological findings of skeletal muscle induced by the myotoxic venom were dilatation of the SR and perinuclear spaces followed by disintegration of myofibrils and mitochondrial swelling, which progressed to dissolution of sarcomeres(Ownby et al., 1976 ; Ownby and Odell, 1983).

If the coma results from drug overdose(sedatives, hypnotics, tranquilizers) or toxins(carbon monoxide, alcohol), hypoxia, acidosis, or hypotension may also impair the musle metabolism(Penn et al., 1972). One patient(case 16) was in a hepatic coma with status epilepticus and the other cases were drowning with coma(case 25) and a myocardiac infarct with cardiogenic shock(case 7). Two patients had markedly increased CK and urine Mb with ARF. The pathogeneis might be impaired muscle metabolism due to hypoxia in cardiogenic shock and drowning. In hepatic coma with status epilepticus it might be due to high fuel-exhaustive muscle exercise. Patients of neuroleptic malignant syndrome may also develop profound muscle necrosis with MU as a consequence of excessive heat production and excessive muscle activity. A direct effect of specific neuroleptics has not been demonstrated. One patient of Parkinson's disease(case 14) with severe high fever of unknown etiology had rigidity, tremulousness and altered mentality. He had taken L-dopa(2 gm per day) and Amantadine(200 mg per day) for 3 years. The pathogenesis suggested a probable forme fruste of neuroleptic malignant syndrome(Delay and Deniker, 1968) due to disordered thermoregulation of hypothalamus, especially in patients receiving levodopa with or without anticholinergics and amantadine(Tanner and Goetz, 1981).

MU has also occurred after prolonged exposure to cold temperatures. ARF resulting from MU has been reported after frostbite(Rosenthal et al., 1981; McNaught et al., 1974). In this study one mountaineer(case 21) was found in coma state with frostbite of distal upper and lower extremity. His CK and urine Mb level were highly increased, followed by ARF. In experimental study(LeBlanc et al, 1981), cold accumulation can be achieved and appears to result in part from adaptations of oxidative systems of skeletal and cardiac muscle that are very similar to those achieved in exercise training. But the precise cause of cold induced MU was not defined.

Heat stroke with MU can also occur in nonexercising individuals. In my patients, one elderly man(case 6) without chronic disease or drug ingestion had heat stroke. His rectal temperature was 41.1C, his CK was 3928 IU, and there was overt MU without ARF. The pathogenesis might be impaired temperature regulation in older individuals, who are particularly vulnerable to heat exhaustion and heat stroke(Schauman, 1972).

One 69 year-old female patient(case 9) in this review had severe hypokalemia(1.8 mEQ/L)with overt MU(303 ng/ml) in hot weather without exhaustive exercise. The mechanism for production of muscle necrosis associated with hypokalemia has been postulated to be ischemia(Knochel and Schlein, 1972) and the resting membrane potential might be lower in this state, with shifts in sodium and chloride ions and small but detectable leakage of CK and Mb(Crawhall et al, 1976), resulting in MU. So MU of this patient might be caused by above mechanisms.

Myoglobulinuric ARF occurred more frequently in high concentration of urine Mb(>300 ng/ml) in this study. It was reported that MU occurred when there was precipitation of Mb in tubular luminal casts(Oliver et al, 1951). Factors other than Mb concentration that affect this precipitation include tubular flow rate(Knochel, 1981) and luminal pH(Clyne et al, 1979) ; the latter may also determine tubular toxicity of the precipitated Mb. But the known major risk factors for the development of ARF are volume depletion, aminoglycoside use, congestive heart failure, and septic shock(Shusterman, et al, 1987). To minimize the chances of development of ARF, routine urine Mb levels should be checked on patients at risk, especially septic shock with hypotension.

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