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Myoglobin Cast Nephropathy, A Series of Five Cases

Sk Md Jaynul Islam*, Iqbal Karim and Shamoli Yasmin

Armed Forces Institute of Pathology, Dhaka Cantonment.

***Correspondence:**
Prof. Dr. Sk Md Jaynul Islam, Department of Histopathology, Armed Forces Institute of Pathology, Dhaka Cantonment, Dhaka, Bangladesh.

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ABSTRACT

Acute kidney injury is a potential complication of severe rhabdomyolysis, which occur mostly due to excessive release of myoglobin from necrosed muscle cells. The major causes of rhabdomyolysis in Indian subcontinent include wasp sting, snake envenomation, strenuous exercise and seizures, etc. The main pathophysiology of AKI due to tubular obstruction, renal vasoconstriction and tubular damage due to myoglobin casts in the tubular lumen. With raised serum creatinine level these patients also show remarkably high serum creatine phosphokinase (CPK). On light microscopy myoglobin casts present as granular eosinophilic pigment casts, sometimes may mimic haemoglobin casts or bile casts. To differentiate the myoglobin casts from other, immunohistochemistry for myoglobin is used in most of the centers worldwide now days. A good number of patients need haemodialysis and most of them recover well, however early diagnosis and timely intervention is warranted. Here we report five cases of myoglobin cast nephropathy in a year at department of histopathology, Armed Forces Institute of Pathology (AFIP), Dhaka, following different non traumatic causes, diagnosed by immunohistochemistry for myoglobin.

Keywords
Myoglobin, Acute Kidney Injury, Immunohistochemistry.

Introduction
Acute kidney injury is a potential complication of severe rhabdomyolysis, regardless of whether the rhabdomyolysis is the result of trauma or some other cause, and subsequently develops renal failure [1]. Rhabdomyolysis is characterized by necrosis of muscle cells and the release of intracellular contents into blood leading to myoglobinuria and elevated muscle enzymes including creatine kinase (CK) in blood. Around 33%–50% of patients with rhabdomyolysis develop acute kidney injury (AKI) [2]. Small quantities of myoglobin present in blood are normally loosely bound to globulins and cannot cross the glomerulus. However if larger quantities of myoglobin are released, this transport system become overwhelmed and myoglobin is filtered through the glomerular basement membrane entering the renal tubules form myoglobin casts may cause tubular obstruction. Myoglobin-induced AKI occurs due to tubular obstruction, renal vasoconstriction, and tubular damage by oxidative injury [3].

Etiology of rhabdomyolysis related myoglobin pigment nephropathy differ in Western and tropical countries. In western countries, exogenous toxins like illicit drugs, alcohol and prescribed drugs are the most common causes. This is followed by muscle diseases, trauma, seizures, immobility and metabolic causes. The major causes of rhabdomyolysis in Indian subcontinent include wasp sting, snake envenomation, strenuous exercise and seizures, etc [4]. Here we report five cases of myoglobin cast nephropathy diagnosed in a tertiary level histopathology center of Dhaka, Bangladesh in one year duration.

Case Series
In Bangladesh renal pathology set up is available in only five organizations, all are in capital city Dhaka. Armed Forces Institute of Pathology (AFIP), Dhaka is one of them, which handle about 800 renal biopsy cases per year. During COVID 19 period in 2020-21 it was declined to almost 50%. During last one year from July 2021 to June 2022, five cases of myoglobin cast nephropathy were diagnosed in the department of histopathology, AFIP, following variable causes. We report here those five cases (Table 1).

Table 1: Demographic, clinical and morphologic findings of cases.

	Case-1	Case-2	Case-3	Case-4	Case-5
Age	41 yrs	49 yrs	22 yrs	50 yrs	66 yrs
Sex	Male	Male	Male	Male	Male
Clinical presentation	Anorexia, nausea,	Anorexia, nausea, oliguria	Oliguria	Oliguria Skin rash	Anuria
Causes	Extensive physical exercise	Unknown	Extensive physical exercise	Bee sting injury	Wasp sting bite
Serum CPK	Increased	Not done	Increased	Increased	Increased
Serum creatinine on admission	2.3 mg/dl	11.07 mg/dl	7.6 mg/dl	10.9 mg/dl	8.4 mg/dl
Urine albumin	nil	trace	nil	1+	nil
Urine RBC	nil	12-15/HPF	nil	nil	nil
AKI stage (KIDGO)	Stage-2	Stage-3	Stage-3	Stage-3	Stage-3
Renal biopsy	G-21 all normal ATI- moderate Regenerative change Pigment casts Interstitium- oedematous	G-14, all normal ATI-moderate Flattening & regenerative change in tubules Pigment casts Interstitiun- oedematous	G-20 all normal ATI- moderate occasional regenerative change in tubule Pigment casts Interstitiun- oedematous with dense lymphocytes	G-18 all normal ATI-moderate Flattening & regenerative change in tubules Pigment casts Interstitiun- oedematous	G-10 all normal ATI-moderate regenerative change in tubules Pigment casts Interstitiun- oedematous
IHC for myoglobin	Positive	Positive	Positive	Positive	Positive
Management	conservative	Dialysis	Dialysis	Dialysis	Dialysis
Outcome	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery

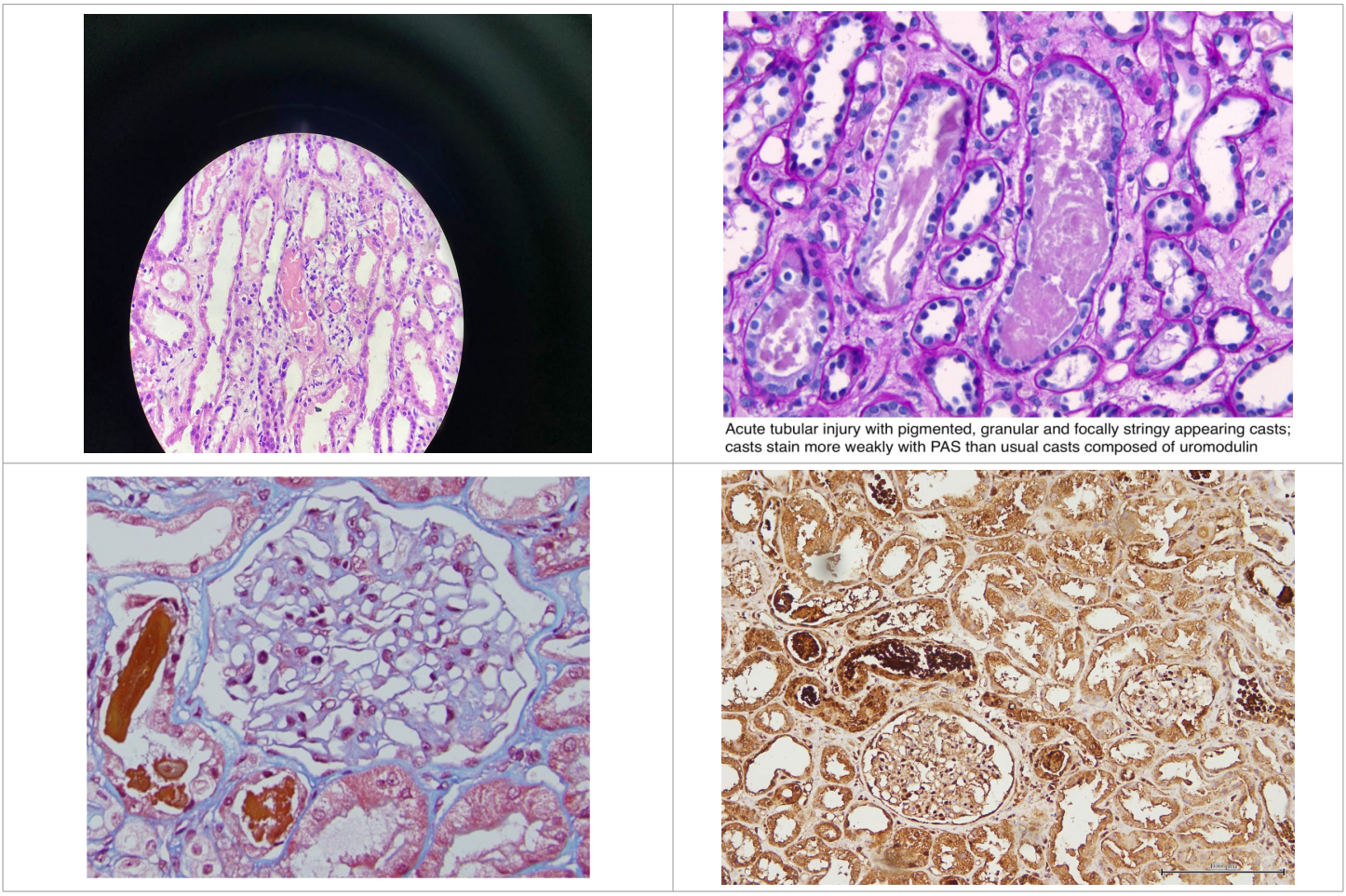

Figure 1: Histopathological findings of myoglobin casts A) H&E, B) PAS, C) Masson trichrome, D) Immunohistochemistry for myoglobin.

Among all the cases the youngest one is of 22 yrs. and the eldest one is of 66 yrs. with average age 45.6 ± 16.0 yrs. All affected cases were male. No definite predisposing factor was revealed in one case, who presented with anorexia and nausea followed by oliguria and rapid raise of serum creatinine level. Among other four, two had the history of strenuous exercise, one bee sting injury and one wasp sting injury.

On investigation most of the cases had raised serum CPK level. The highest serum creatinine level was found in case no 2 (11.07 mg/dl), whose definite etiological factor could be known. The lowest serum creatinine level was found in case no 1 (2.3 mg/dl) which was initiated by strenuous physical exercise. The average serum creatinine level was 8.05 ± 3.5 mg/dl. Only case no 2 had haematuria and other four cases have not shown any red cell passing through urine. Most of the cases do show proteinuria, only case no 2 and 4 had trace to 1+ proteinuria. During biopsy case no 1 was in KIDGO AKI stage-2 and all other were in KIDGO AKI stage-3.

On histopathology of renal biopsy, all had adequate number of glomeruli absolutely normal looking, without any global or segmental sclerosis. All the cases show focal granular reddish-brown pigment casts in the tubules. On PAS staining the casts were weakly positive and on masson trichrome staining casts were bright red. There are diffuse flattening of tubular epithelial cells with focal swollen tubular cell and regenerative changes. On immunohistochemistry the pigment casts were positive for myoglobin. Stage 3 cases were managed by dialysis and stage 2 was managed with conservative therapy. All the patients were recovered well (Figure 1).

Discussion

Rhabdomyolysis is a clinical syndrome following injurious insults to muscles including physical, thermal, toxic, infective, metabolic, ischaemic and inflammatory insults. The final step of the skeletal muscle breakdown is the release of toxic intracellular components, such as myoglobin, into the circulation [1,5]. The renal threshold for myoglobin is 0.5 -1.5 mg/dl above which it appears in the urine. When a large amount of myoglobin enters the tubular lumen they precipitate with Tamm-Horsfall protein to form myoglobin casts especially in acidic urine [6].

Myoglobin is cytotoxic, activating both pro-oxidant and inflammatory pathways. Cytotoxicity is augmented in the presence of volume depletion and aciduria [7]. Renal vasoconstriction, tubular obstruction and apoptosis also contribute in pathological processes in myoglobin toxicity. Myoglobin possesses a haem centre that can catalyse the production of free radicles within the kidneys. The haem group within myoglobin is capable of cycling between various oxidative states that may lead to lipid peroxidation independently of the Fenton reaction and iron release [8]. As the pathogenesis of rhabdomyolysis is multifactorial, the role of other concomitant factors, cannot be ignored. In our series two cases caused by strenuous physical exercise, one following bee sting injury and one after wasp sting injury. In one case no definitive cause could be revealed.

In myoglobin cast nephropathy, light microscopy shows features of acute tubular injury (ATI) with attenuation of tubular epithelial cells, cytoplasmic vacuoles, brush border loss and sloughed out intratubular epithelial cells [9]. Myoglobin casts are usually appear eosinophilic to brown granular in hematoxylin and eosin stain, weakly PAS positive and bright red in Masson trichrome stain. Myoglobin casts have to be differentiated from other pigment casts like haemoglobin casts and bile casts. There are no morphological characteristics to differentiate myoglobin casts from hemoglobin casts. Therefore, immunohistochemical staining for myoglobin or haemoglobin is required to confirm the diagnosis [10]. We got myoglobin casts in all the cases, which were confirmed by immunohistochemistry for myoglobin.

Prognosis of rhabdomyolysis induced AKI is usually good. Though most of our patients presented with AKI with high creatinine levels that required haemodialysis, all of them recovered very well. In a series of 46 patients reported by Sakthirajan R et al., 45 (97.8%) required haemodialysis, 3 (6.5%) died of sepsis/disseminated intravascular coagulation and 5 (12%) proceeded to chronic kidney disease (CKD) [6].

Conclusion

Myoglobin cast nephropathy though rare but one of the important cause of AKI. For early intervention definitive diagnosis is essential as such immunohistochemistry for myoglobin should be performed for confirmation.

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