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# Clinicopathological study of pigment induced nephropathy; a retrospective study

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## ABSTRACT

*Introduction:* Rhabdomyolysis and hemolysis cause pigment nephropathy that progresses to chronic kidney disease (CKD) requiring hemodialysis in some patients. As this is a significant financial burden, understanding the etiologies and renal biopsy findings aids in timely diagnosis and optimizing outcomes.
*Objectives:* We analyzed the etiology, clinicopathological features, and renal outcome of seventeen patients with pigment nephropathy.
*Patients and Methods:* This retrospective study was conducted from 2018 to 2021. Data on detailed clinical history, laboratory parameters, renal biopsy records and the renal outcome was collected.
*Results:* Among seventeen patients with pigment nephropathy, the etiology was rhabdomyolysis in 15 patients and hemolysis in two patients. Oliguria was the most common clinical presentation, and all patients presented with acute kidney injury (AKI). Renal biopsy revealed reddish beaded granule and vermiform-like casts in 10, brownish casts with intra-tubular hemosiderin in three, and granular and calcific casts in two patients each. While fourteen patients recovered to normal renal function within three months, one progressed to stage 5 CKD, one had stage 2 CKD, and one died.
*Conclusion:* In most patients, clinical history did not reveal a direct diagnosis of rhabdomyolysis, and hence one must remain vigilant even in the absence of the classical triad of symptoms.

Original Article

*Implication for health policy/practice/research/medical education:*
In a retrospective study, we analyzed the etiology, clinicopathological features and renal outcome of seventeen patients with pigment nephropathy. Our results suggest that mortality is significantly lower in our series compared to other series. It also adds to the literature that early diagnosis and intense follow-up can help complete renal function recovery in most patients with pigment-induced nephropathy.
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## Introduction

Pigment-induced nephropathy leads to a rapid reduction in kidney function due to the deposition of endogenous heme-containing proteins: myoglobin and hemoglobin. Following glomerular filtration, these pigments get absorbed by the proximal convoluted tubule and cause tubular obstruction, renal vasoconstriction, and increased oxidative stress, resulting in acute renal failure (1). Prognosis is dependent on etiological factors, with a few patients progressing to chronic kidney disease (CKD) (2). Hence, a thorough knowledge of etiological and histopathological factors supported by immunohistochemistry is required for correct diagnosis.

## Objectives

There are few studies on clinical profile and the outcome in patients with pigment-induced nephropathy; we sought to analyze the clinicopathological characteristics and renal outcome in such cases.

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## Patients and Methods

### *Study design*

We conducted a retrospective study from January 2018 to June 2021. After an ethical clearance from the institutional ethics committee, the renal biopsy register and records were reviewed, and patients with pigment-induced nephropathy were included in the study. Patients with primary glomerular diseases, inadequate renal biopsies, cases without myoglobin immunohistochemistry, and those lost to follow-up within three months of the initial biopsy were excluded. A total of seventeen patients were identified in the study period. Detailed clinical history for various hemolysis or rhabdomyolysis causing aetiologies - recent trauma, exertion, seizures, infections, and alcohol/medications intake was obtained from medical records. Additionally, serum creatinine levels (at hospitalization and every follow-up), urine protein, and spot urine protein: creatinine ratios were retrieved. Plasma hemoglobin concentration, fragmented red cells, reticulocyte count, serum lactate dehydrogenase levels, and serum creatine phosphokinase (CPK) were noted.

Renal biopsies were stained with hematoxylin and eosin, periodic acid Schiff (PAS), Masson's trichrome, and periodic acid silver methenamine and reviewed separately by two renal pathologists. Accordingly, glomeruli, tubules, and interstitial and vascular compartments were studied for pathologic changes. The acute tubular injury was graded as mild, moderate, and severe, depending on the percentage of tubules affected. Cases with reddish-brown/granular casts, intra-tubular hemosiderin, and vermiform casts were stained with Perls' Prussian blue (PPB), resulting in blue granular staining of the tubular cytoplasm. Even the intra-tubular casts stained blue, indicating positivity.

Myoglobin immunohistochemistry (PathnSitu, rabbit monoclonal antibody, CA84566 USA) was conducted in all cases. The degree of positivity to myoglobin was assessed as 1+ for 1-10 positive casts, 2+ for 10-15 casts, and 3+ to 4+for more than 20casts (3). Positive controls (skeletal muscle) and negative controls were used in all batches. Direct immunofluorescence for a panel of antisera containing IgG, IgA, IgM, C3, C1q, kappa, and lambda (FITC-conjugated rabbit antihuman antisera manufactured by DAKO from Denmark) was performed in all cases.

### *Statistical analysis*

The data were entered in excel sheets with an exclusive code assigned to all non-available/not reported data. Statistical analysis was done using IBM SPSS version 25. Continuous variables were expressed as mean and standard deviations if normally distributed and median with an interquartile range for non-normally distributed. Categorical variables were expressed as frequencies and percentages.

## Results

Nine patients were males and eight females. Age ranged from 13 to 61 years (mean; 39 years). Fifteen patients (88%) showed rhabdomyolysis due to drugs (9 cases), trauma (3 cases), malignant hyperthermia (2 cases), and sepsis (one case). Two patients showed hemolysis due to paroxysmal nocturnal hemoglobinuria (PNH) and long-term warfarin therapy superimposed on a prosthetic heart valve (Table 1).

All patients presented with oliguria (100%) and had acute kidney injury (AKI). Serum creatinine ranged from 4.21-16.5 mg/dL, with about half showing proteinuria. A direct suggestion of pigment nephropathy was found in only two patients (one patient with HIV treatment and

**Table 1.** Demographic parameters and etiologic factors

| Case no | Age | Gender | Clinical diagnosis | Etiologic factors |
|---|---|---|---|---|
| 1 | 29 | F | AKI III | Sepsis |
| 2 | 40 | F | AKI III | Drug induced (Rifampicin) |
| 3 | 58 | M | AKI III | Drug induced (Tenofovir) |
| 4 | 19 | F | AKI III | Malignant hyperthermia |
| 5 | 55 | M | AKI III | Drug induced (Homeopathy) |
| 6 | 30 | F | AKI III | Drug induced |
| 7 | 20 | M | AKI III | Trauma-heavy exercise |
| 8 | 50 | F | AKI III | Drug induced (Ayurvedic) |
| 9 | 25 | F | AKI III | Drug induced (Rifampicin) |
| 10 | 13 | M | AKI III | Lathi charge by police |
| 11 | 48 | F | AKI III | Trauma |
| 12 | 61 | M | AKI III | Drug induced (Tenofovir) |
| 13 | 23 | M | AKI III | Malignant hyperthermia |
| 14 | 22 | M | AKI III | Crab bite |
| 15 | 48 | M | AKI III | Drug induced (Warfarin induced) |
| 16 | 28 | M | AKI III | PNH |
| 17 | 48 | F | AKI III | Drug induced (Tenofovir) |

AKI, Acute kidney injury stage III; PNH, Paroxysmal nocturnal hemoglobinuria.

another with haemolytic anemia). Urine examination for myoglobin was available in three of fifteen patients with rhabdomyolysis. However, only one showed the presence of myoglobin.

The average number of glomeruli was 12, with the number of obsolete glomeruli ranging between 1 and 5. Glomerular morphology was normal in all cases. Dilated tubular lumen, simplification of lining epithelium, loss of brush border, and cytoplasmic vacuolation were noted in all the biopsies (Table 2).

On light microscopy, casts were stained dark pink to bright red with PAS, bright red with Masson's trichrome, and brown to black with methenamine silver (Figure 1). There was neither a fractured appearance of casts nor a giant cell reaction around the casts. Casts did not show light chain restriction with direct immunofluorescence. There were no immunoglobulin deposits and complements in glomeruli or along tubular basement membrane in all cases. Electron microscopy was not performed in any of the cases.

Atypical casts were positive for myoglobin in fifteen patients, grade 1+ in fourteen cases (93%) and grade 2+ in one case (7%). Myoglobin staining was solid, mainly within the proximal tubular lumina. Two cases revealed intra-epithelial staining and positivity within the detached cells of the tubular lumen too.

In two cases, atypical casts and intra-tubular hemosiderin revealed positivity with PPB. In both cases, myoglobin was absent in the atypical casts. Immunohistochemistry (IHC) for hemoglobin was not conducted due to financial constraints.

While fourteen patients recovered and attained baseline creatinine (0.8-1.3 mg/dL) within three months of the onset of illness, one patient with concurrent diabetic kidney disease class III and moderate interstitial fibrosis and tubular atrophy (IFTA), progressed to stage 5 CKD with dialysis dependence over subsequent six months. Another patient with tenofovir-induced AKI III recovered partially and remained in stage II CKD. A 58-year-old male patient on antiretroviral therapy (ART) for the last 20 years was recently changed to tenofovir-based ART. He was admitted with rhabdomyolysis and died due to sepsis-induced multi-organ dysfunction.

**Table 2.** Renal biopsy findings

| Biopsy finding | No. of cases , n (%) |
|---|---|
| Average number of glomeruli; range | 12 ; 1-28 |
| Cases with obsolete glomeruli | 4 (23%) |
| Reddish beaded granule like casts, vermiform casts | 10 (76%) |
| Brownish casts, intratubular hemosiderin | 3 (17%) |
| Granular casts | 2 (11%) |
| Calcific casts | 2 (11%) |
| Severe ATI | 9 (52%) |
| Moderate ATI | 8 (47%) |
| Eosinophils in interstitium | 10 (58%) |
| Neutrophils in interstitium | 5 (29%) |
| IFTA | |
| Nil | 3 (17.5%) |
| Minimal | 13 (76.5%) |
| Moderate | 1 (6%) |

ATI, Acute tubular Injury; IFTA, Interstitial fibrosis and tubular atrophy

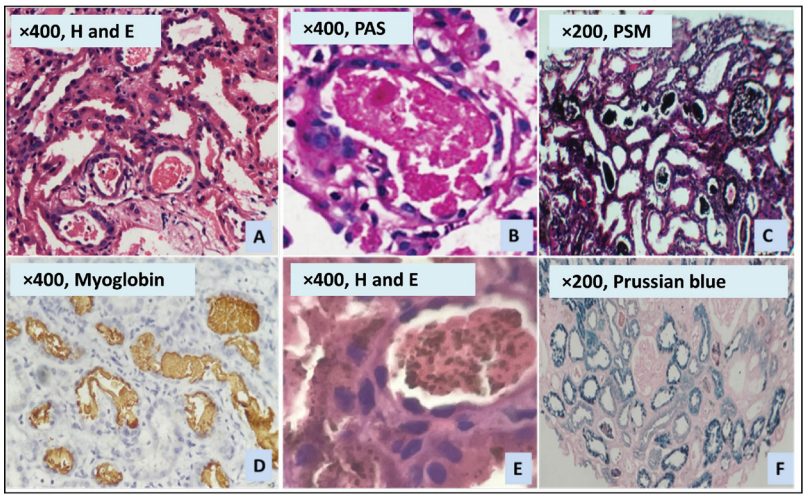


**Figure 1.** Histomorphology findings in pigment induced nephropathy. (A) Reddish granular and vermiform casts, (B) Bright magenta-coloured casts, (C) Argyrophilic intratubular casts stained with Periodic acid silver methenamine (PSM), (D) Myoglobin positive casts in immunohistochemistry, (E) Intratubular and luminal hemosiderin, (F) Intratubular and luminal hemosiderin confirmed with Pearls Prussian Blue stain (PPB).

## Discussion

Pigment nephropathy represents one of the most severe complications of rhabdomyolysis or hemolysis following the deposition of endogenous heme-containing proteins in the kidneys and causes an abrupt decline in renal function. Rhabdomyolysis results from physical, metabolic, toxic, thermal, ischaemic, and infective/inflammatory insults to muscles (3). The skeletal muscle breakdown causes the release of toxic cellular substituents, such as myoglobin, into the circulation (4). On the other hand, intravascular hemolysis occurs in idiosyncratic drug reactions, PNH, hemorrhagic fevers, and septic shock releases heme (2).

In most patients in our study, the cause of pigment nephropathy was rhabdomyolysis. Drug administration, trauma, malignant hyperthermia, and sepsis were the causative factors which is in line with other studies that reported drug abuse, trauma, strenuous exercise, and infectious diseases (1,5). One patient had snake bite-induced nephropathy. The phospholipase A2 in the snake venom causes injury to the skeletal muscle (6). Snakebite, quite common in India, was the leading cause of rhabdomyolysis in previous studies (1,7).

Exertional and traumatic rhabdomyolysis are commonly caused due to continuous contractions of the muscle compromising the capillary blood flow while the resulting muscle hypoxia leads to rhabdomyolysis (7). Two such cases in the present study match similar aetiologies detected in others (7). In addition, two patients had a history of seizures. The intense muscular activity during seizures depletes the available energy within the muscle to disrupt it (8).

Paroxysmal nocturnal hemoglobinuria is a rare disorder, with the defective Pig-A causing a triad of symptoms, namely haemolytic anemia, pancytopenia, and thrombosis, thereby causing iron deposition in the kidneys (9). In one patient each, PNH and warfarin usage led to hemolysis. Both demonstrated renal hemosiderosis, and one had AKI, correlating with previous case reports that demonstrated AKI and CKD due to PNH (9). In a study of 14 PNH patients by Ram et al, AKI was noted in six (42.8%) patients (10).

Acute kidney injury is a complex disorder with a minute elevated serum creatinine to anuric renal failure. It is often associated with severe consequences, including death (11). Surgery, trauma, and medical causes like sepsis, dehydration secondary to diarrhea, and vomiting are the most common etiological factors of AKI, requiring hemodialysis (12). Four patients with AKI in our study had vomiting and loose stools

According to previous literature, around 10%–50% of patients with rhabdomyolysis develop AKI, contributing to 5%–25% of all cases of AKI (13,14). In a retrospective study involving 126 patients with severe rhabdomyolysis, the incidence of AKI was 58% (5). In the present study, 65% of rhabdomyolysis patients showed AKI.

Drug-induced rhabdomyolysis was the most common cause of myoglobinuric AKI. Tenofovir-induced rhabdomyolysis was seen in three HIV patients on TLE (tenofovir, lamivudine and efavirenz) regimen. Rhabdomyolysis in HIV infection could result from viral or opportunistic infections or antiretroviral drugs (15). Tenofovir resulted in myoglobinuric AKI in 5% of HIV-infected patients (16). Risk of nephrotoxicity is further increased with advanced HIV infection and other drugs-acyclovir or statins (17). CPK levels were elevated in a patient on tenofovir medication (18). All three patients in our study presented with AKI after ten days of initiation of the TLE regimen. CPK was elevated in all of these patients.

Serum CPK is the most sensitive enzyme marker of muscle injury, with values >5000 IU/L known to increase AKI risk (1). A considerable disparity in the serum CPK levels ranging from 4700-30700 IU/L was noted among our patients, which could be due to the difference in the severity of rhabdomyolysis and timing of renal biopsy. As compared to previous studies, the etiological and renal outcome in our study is shown in Table 3.

Renal biopsy findings of our patients revealed moderate and severe acute tubular necrosis (ATN) in 8 and 9 patients, respectively. Reddish beaded granule-like casts and vermiform casts were found in 10 patients; brownish casts with intra-tubular hemosiderin in three patients; granular and calcific casts in 2 each. Eosinophilic infiltration was found in 10. A comparison of renal biopsy findings is given in Table 4.

Treatment strategies for pigment nephropathy include-immediate intravenous volume repletion, prevention of myoglobin/hemoglobin cast formation, optimal crystalloid selection with urine alkalinization, and haemodialysis (19,20). We provided symptomatic treatment and hemodialysis until final recovery for most patients. In addition, anti-snake venom for snakebite and anti-epileptics for those with seizures were given.

An increased risk of CKD has been demonstrated in AKI patients irrespective of their recovery (9,21,22). While 14 patients recovered and attained baseline creatinine levels in our study, two progressed to CKD, and one patient died. Of two patients with CKD, one was diabetic and had class III diabetic kidney disease, moderate IFTA, moderate to severe ATN, and high serum creatinine and creatinine phosphokinase levels. Similarly elevated serum creatinine and CPK, with stage III AKI and severe ATN, were found in the only patient who died.

In a previous study by Sakthirajan et al, five out of 46 patients progressed to CKD (1). Another study by Liapis et al illustrated full recovery and CKD in 45% each,

**Table 3.** Comparison of the etiological factors and renal outcome in our study with that of other studies

| | Present study | Liapis et al | Sakthirajan et al | Jhansi et al |
|---|---|---|---|---|
| No of patients | 17 | 214 | 46 | 57 |
| Age in years | 39 (13-61) | 48.9 ± 18.3 | 40.15 ± 12.3 | 34.47 (17-77) |
| Gender | 9 males, 8 females | 138 males and 76 females | 65% males, 35% females | 49 males, 8 females |
| Average serum creatinine | 11.65 ± 5.36<br>Range: 4.21 to 16.5 mg/dL | 10.3 ± 15.5;<br>Range: 1.0-45.0 | 7.5 ± 2.2 | 8.4; range= 1.7 to 20.8 (in mg/dL) |
| Average CPK | 16,294 IU/L | 16586 IU/L | 2319 IU/L | 2410 IU/L |
| Rhabdomyolysis | 88.2% | 100% | 64% | 100% |
| Hemolysis | 11.8% | 0 | 36% | 0% |
| Etiological factor | Rhabdomyolysis<br>Drugs=09<br>Trauma= 03<br>Malignant hyperthermia= 02<br>Sepsis= 1<br>Hemolysis<br>Warfarin induced=1<br>PNH=1 | Drug induced= 26<br>Trauma= 15<br>Intense physical activity= 3<br>Sepsis= 9 | Rhabdomyolysis<br>Snake envenomation= 10<br>Seizures =7<br>Strenuous exercise= 5<br>Wasp sting= 2<br>Rifampicin induced= 2<br>Hemolysis<br>Rifampicin induced= 7<br>Sepsis= 5<br>Malaria= 3<br>Mismatched blood Transfusion= 3<br>PNH= 2 | Snake envenomation= 12<br>Exertional=11<br>Seizures =7<br>Wasp sting= 5<br>Drug induced= 4<br>Sepsis= 2<br>Hyperpyrexia= 2 |
| Outcome at follow-up | 14= recovered<br>2= CKD<br>1=died | 5= deceased<br>10=full recovery<br>9= CKD<br>2=dialysis dependent<br>1= 2nd transplant | 5= CKD<br>3=died with sepsis/ disseminated intravascular coagulation | Most of them returned to normal. |

CPK, Creatine phosphokinase; PNH, Paroxysmal nocturnal hemoglobinuria; CKD, Chronic kidney disease.

**Table 4.** Comparison of renal biopsy findings

| | Present study | Liapis et al | Sakthirajan et al |
|---|---|---|---|
| No. of cases | 17 | 214 | 46 |
| Acute tubular injury | All | All | All |
| Nature of pigment casts | Reddish beaded, calcific casts, vermiform casts, reddish brown pigment casts | Pink, translucent, red, refractile brownish red | NA |
| Intratubular hemosiderin | 17% (3) | NA | NA |
| Neutrophil casts | 29% (5) | NA | NA |
| Interstitial eosinophils | 58.8% (10) | 25% (53) | 14/46 |
| Calcium oxalate crystals | 11% (2) | 20% (42) | NA |
| IFTA-minimal | 76% | 100% | NA |

Numbers in parentheses represent number of cases.
IFTA, Interstitial fibrosis and tubular atrophy; NA, Not available.

among whom 18% died (23).

## Conclusion

A wide variety of etiological factors causing rhabdomyolysis and hemolysis result in pigment nephropathy. As seen in our study, the classic triad of symptoms and a precise diagnosis are often absent. Thorough knowledge of the etiological factors and clinicopathological presentation and confirmation from the Immunohistochemistry results help in early detection and timely intervention.

## Limitations of the study

Our investigation is a retrospective study with a small sample size from only two centres. The non-availability of urine myoglobin and plasma-free hemoglobin values are additional limitations.

## Authors' contribution

**Conceptualization:** Ranjana Shashidhar Ranade, Atul Desai, Mahabaleshwar Harikrishna Mayya.
**Data curation:** Ranjana Shashidhar Ranade, Atul Desai, Manjunath Revanasiddappa.
**Formal analysis:** Ranjana Shashidhar Ranade, Atul Desai, Mahabaleshwar Harikrishna Mayya, Sanjay Timmanagouda Patil.
**Investigation:** Ranjana Shashidhar Ranade, Atul Desai, Mahabaleshwar Harikrishna Mayya.
**Methodology:** Ranjana Shashidhar Ranade, Atul Desai, Mahabaleshwar Harikrishna Mayya, Sanjay Timmanagouda Patil.
**Project administration:** Manjunath Revanasiddappa.
**Resources:** Ranjana Shashidhar Ranade, Atul Desai, Mahabaleshwar Harikrishna Mayya, Sanjay Timmanagouda Patil.
**Supervision:** Manjunath Revanasiddappa.
**Validation:** Manjunath Revanasiddappa, Ranjana Shashidhar Ranade, Hephzibah Rani, Mahabaleshwar Harikrishna Mayya.
**Visualization:** Sanjay Timmanagouda Patil, Hephzibah Rani, Ranjana Shashidhar Ranade, Mahabaleshwar Harikrishna Mayya.
**Writing–original draft:** Ranjana Shashidhar Ranade, Hephzibah Rani, Mahabaleshwar Harikrishna Mayya, Manjunath Revanasiddappa.
**Writing–review & editing:** Ranjana Shashidhar Ranade, Atul Desai, Manjunath Revanasiddappa.

## Conflicts of interest

The authors declare that they have no competing interests.

## Ethical issues

This retrospective study review was conducted in accord with the World Medical Association Declaration of Helsinki. The institutional ethical committee at SDM University approved all the study protocols (SDMCDS IEC No. 2021/Medical/Pathology/S/01). Accordingly, written informed consent was taken from all participants before any intervention. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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