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Original contribution

Myoglobin casts in renal biopsies: immunohistochemistry and morphologic spectrum☆

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Summary Five hundred eighty renal biopsies from a pool of 27 850 archived cases were identified in which a myoglobin stain was performed because of atypical casts. Two hundred and thirty-eight (41%) of these biopsies were found to be positive for myoglobin casts. The morphology of the myoglobin casts ranged from light, almost translucent and refractile, to pink, to dark red and slightly brown granular casts by hematoxylin and eosin, to beaded globular casts that stained brightly fuchsinophilic with Masson trichrome and partially argyrophilic with silver methenamine. All biopsies displayed acute tubular injury associated with intratubular debris and thinning and vacuolization of tubular epithelium. Approximately 20% of myoglobin-positive biopsies showed calcium oxalate or phosphate deposition. Positive myoglobin staining was present in casts, proximal tubular epithelial cells without casts, and also dehisced epithelial cells. Collecting ducts and occasionally the distal tubular epithelium also stained positive. One case showed concurrent myeloma cast nephropathy with "fractured" casts and translucent myoglobin-positive casts. Herein, we describe the morphologic spectrum of myoglobin-positive casts. We conclude that utilization of myoglobin immunohistochemistry is advantageous and, when not available, knowledge of the morphologic spectrum is important.

1. Introduction

Rhabdomyolysis is reported to be the underlying cause of acute renal failure in 7%-15% of all cases in the United States [1,2]. Rhabdomyolysis is associated with the release of myoglobin into the circulation, filtered freely by the glomeruli and forming tubular casts. Myoglobin casts can be problematic to diagnose on light microscopy and can mimic paraprotein casts. Most clinical series of rhabdomyolysis with myoglobinemia are case reports or small series from the older literature, and only a few studies demonstrate the presence of myoglobin in a kidney biopsy [3–7]. Many pathologists do not use myoglobin immunohistochemistry (IHC). We sought to analyze a large series of renal biopsies to determine the spectrum of morphologic findings of myoglobin casts and evaluate the utility of the myoglobin stain.

2. Materials and methods

All kidney biopsy records in our institution from the beginning of 2011 through June 2014 in which a myoglobin stain was performed were reviewed. This retrospective review was an exempt study according to Institutional Review Board 45CFR 46.101(6) (4). The renal biopsy and clinical findings at the time of the renal biopsy were analyzed. The biopsies were received from multiple medical centers across the

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United States, thought to show a fair representation of nephrology practice settings ranging from small community practice groups to tertiary care referral centers. Among a total 27 850 renal biopsies in our service, there were 580 cases in which IHC for myoglobin was ordered because of morphologically suspicious or atypical casts and/or clinical findings suspicious for myoglobin-related renal injury. Two hundred and thirty-eight (41%) of these biopsies were found to be positive for myoglobin casts by the initial renal pathologist. Among these, 12 were renal allograft biopsies. All of the 238 cases initially identified with myoglobin-positive casts were reevaluated by 3 of the authors (H. L., R. H., and F. S.). Twelve cases with no positive casts and only minimal proximal tubular brush border staining were excluded. Another 12 cases in which the myoglobin IHC stain was missing and or a repeat myoglobin IHC failed to show myoglobin staining casts in the deeper levels were also excluded. Excluding the 24 cases noted above, we identified a total of 214 cases with definitive casts, which were included in this study.

Two antibodies to myoglobin were used: Dako (Carpentaria, CA) from January 1, 2011, through March 30, 2012 (until this source was no longer available), and Cell Marque (Rocklin, CA) from March 12, 2012, through June 30, 2014. The 2 antibodies stained identically as evidenced by the positive controls (skeletal muscle). A negative control was included in all batches to determine background staining. The degree of positive myoglobin casts was semiquantitatively assessed on a scale of 1+-4+ as follows: 1+ showed 1-10 positive casts, 2+ showed 10-15 casts, and 3+-4+ showed more than 20 casts. The consecutive slides for hematoxylin and eosin (H&E), Periodic acid–Schiff reaction (PAS), silver methenamine, and trichrome were evaluated in conjunction with the myoglobin stain with special attention to myoglobin-positive casts.

Follow-up data were available in 27 of 214 patients.

3. Results

3.1. Clinical findings

The average age of the 214 patients with positive myoglobin casts was 48.9 years ± 18.3 SD (range, 2-88 years). There were 138 males and 76 females. All patients presented with acute renal failure (average serum creatinine, 10.3 ± 15.5; range, 1.0-45.0) (Table 1).

In the majority of patients in this series, the history did not mention rhabdomyolysis and/or myoglobinuria was not listed in the laboratory findings. In a smaller number of patients (35), there was direct mention or suggestion of clinical findings suspicious for rhabdomyolysis (average creatine phosphokinase [CPK], 16 586 IU/L; range, normal–335 000 IU/L). Two patients had normal CPK levels. All patients clinically had acute renal failure. A variety of known etiologies of the rhabdomyolysis (Table 2) and numerous comorbidities were identified; 41% of the patients with myoglobin casts presented with moderate to severe hypertension. Many of the patients, especially the older patients, had other underlying kidney diseases. These included infection, polydrug substance abuse, adverse medicinal reactions, dehydration, seizures, sepsis, intense exercise, and trauma. Preexisting renal diseases included systemic lupus erythematosus, immunoglobulin A nephropathy, plasma cell dyscrasia, amyloidosis, diabetic nephropathy, hypertensive vascular disease, and anti-Glomerular Basement Membrane disease.

Table 1 Clinical and laboratory data of 214 patients

Data	Values
Demographics	
Age	
Range	2-88 years
Mean	48.9 ± 18.3
Sex	
Male	138
Female	76
Serum creatinine at biopsy	
Mean	10.3 ± 15.5 mg/dL
Range	1.5-45.0
Creatine phosphokinase (35 patients)	
Mean	16 586 IU/L
Range	normal–335 000 IU/L

3.2. Morphologic findings

All cases displayed evidence of acute tubular injury most often with marked thinning of the tubular epithelium and tubular epithelial vacuolization. In fact, the acute tubular injury was

Table 2 Underlying etiologies in this series

	Etiology/preexisting conditions	No. of cases
1	Drug administration (polydrug abuse, cocaine, heroin, opium, opioids)	26
2	Obtunded (falling, traffic injury, found unconscious, etc)	15
3	Dehydration	14
4	Infection	13
5	Transplantation	12
6	Seizures	10
7	HIV patients	10
8	Sepsis	9
9	Pancreatitis	5
10	Chemotherapy (eg, for cancer)	4
11	Myopathies	3
12	Intense physical activity (marathon runners)	3
13	Postsurgery	3
14	Malignant hypertension	2
15	Wasp stings	2
16	Multiorgan failure	2