Glomerular haematuria, renal interstitial haemorrhage and acute kidney injury

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Abstract
Macroscopic haematuria of glomerular origin has been associated with acute kidney injury. We report a patient with IgA nephropathy, macroscopic haematuria and acute kidney injury. Systemic anticoagulation may have aggravated haematuria. There was extensive interstitial and intratubular red blood cell extravasation, and interstitial haemosiderin deposits. The abundant presence of macrophages expressing the haemoglobin scavenger receptor CD163 and of cells stained for oxidative stress markers (NADPH-p22 phox and heme-oxigenase-1) in areas of interstitial haemorrhage and red blood cell cast-containing tubules provided evidence for a role for free haemoglobin in tubulointerstitial renal injury in human glomerular disease.

Keywords: acute renal failure; haematuria; IgA nephropathy; interstitial haemorrhage

Case report
A 51-year-old woman was admitted for AKI. She had a past history of rheumatic fever, aortic and mitral replacement surgery in 1997, tricuspid insufficiency, and chronic atrial fibrillation treated with digoxin and acenocoumarol.

Five weeks before admission, she consulted for back pain and fever. Urinalysis showed dipstick proteinuria, pyuria and haematuria. Serum creatinine (sCr) was 0.8 mg/dL. Oral levofloxacin was prescribed. Urine culture was negative. Two weeks before admission, she noticed dark urine that persisted at the time of admission.

Physical examination revealed blood pressure 130/70 mmHg and moderate oedema in lower extremities. The laboratory findings were as follows: haemoglobin (Hb) 11.6 g/dL, WBC 6500 (92% neutrophils and 0.8% eosinophils), platelets 175 000 and sCr 8.6 mg/dL. Prothrombin time international normalized ratio (INR) 6.2. Urinalysis results are: proteinuria 2.9 g/24 h and haematuria.

Renal Doppler ultrasound showed a 128-mm right kidney and 137-mm left kidney, increased parenchymal echogenicity, poor cortico-medullar differentiation, and elevated Doppler resistive index.

Antinuclear, anti-GBM and anti-neutrophil cytoplasmic antibodies were negative. IgA was 220 mg/dL, IgG was 1217 mg/dL, IgM was 107 mg/dL, C3 was 116 mg/dL, C4 was 22 mg/dL and no monoclonal immunoglobulins were detected. Serology was negative for HVB, HVC and HIV. Other findings were LDH >1000 IU/L, serum albumin 3.1 g/dL and total cholesterol 171 mg/dL.

IV methylprednisolone (total dose 2 g) and then oral prednisone 1 mg/kg/day were prescribed (Figure 1C). A focal necrotizing lesion was evidenced in one glomerulus. Immunofluorescence (IgG, IgA, IgM, C3, C1q, Kappa and Lambda) revealed granular mesangial IgA and C3 depos-
Fig. 1. Renal biopsy glomerular findings. (A) Moderate mesangial proliferation and increased mesangial matrix (H&E). (B) Immunofluorescence: granular mesangial IgA deposits (original magnification ×200. (C) Evolution of serum creatinine and timing of renal biopsy and therapy for IgA nephropathy. Mpred, methylprednisolone; Pred, prednisone; Bx, renal biopsy; CFM, cyclophosphamide.
its. Tubular degenerative and regenerative changes were consistent with acute tubular necrosis. There were remarkable interstitial RBC extravasation, RBC casts in most tubules and interstitial haemosiderin deposits (Figure 2). CD163-expressing macrophages infiltrated the renal interstitium near haemorrhage areas. The NADPH oxidase p22 phox subunit and heme-oxygenase-1 (HO-1) were expressed in haemorrhage areas of the cortex and outer medulla. Interstitial macrophages, and T- and B-lymphocyte infiltration were present (Figure 2), but neutrophils were absent (not shown). AKI secondary to macroscopic haematuria due to IgAN was diagnosed. Prednisone was tapered, and acenocoumarol reinitiated. A second macroscopic haematuria episode was associated with deterioration of renal function, and

Fig. 2. Renal biopsy tubulointerstitial findings. (A) Cortical interstitial haemorrhage and intratubular red blood cell (RBC) casts (haematoxylin and eosin). (B) Perl’s blue stains interstitial haemosiderin deposits (in blue, arrows). (C–H) Immunohistochemistry: (C) cluster of differentiation-163, (D) cluster of differentiation-68-positive macrophages, (E) nicotinamide adenine dinucleotide phosphate-p22 phox subunit, (F) heme oxygenase-1, (G) cluster of differentiation-3 T cells and (H) cluster of differentiation-20 B cells. Cluster of differentiation-163 expression and oxidative stress (nicotinamide adenine dinucleotide phosphate-p22 phox and heme oxygenase-1) are mainly related to renal interstitial haemorrhage, while heme oxygenase-1 was also present in tubular cells, especially in cells lining tubules containing red blood cell casts (arrows). In areas of interstitial haemorrhage, there was an inflammatory infiltrate consisting mainly of T cells and macrophages (original magnification, ×200).
500 mg cyclophosphamide was administered (Figure 1C). Haematuria and renal function improved, and sCr was 1.3 mg/dL at the last follow-up.

Discussion

The incidence of AKI during macroscopic haematuria episodes in IgAN ranges from 1.2% to 35% [2,4]. Mean time to peak sCr is 6–15 days after haematuria onset, and the average duration of haematuria is 15–60 days. sCr decreased 2–45 days after haematuria cessation [2,4]. Recovery of renal function is incomplete in 25% of the patients. The severity of acute tubular necrosis and worse outcome correlates with duration of haematuria. Patients who stopped or decreased their RBC casts correlate with worse outcome [3]. The duration of macroscopic haematuria, the absence of previous macroscopic haematuria episodes, age >50 years, and higher baseline sCr increase the risk of incomplete recovery of renal function. Glomerular crescents were present in a low percentage of glomeruli (<20% of glomeruli) in all series, and this percentage was higher in patients who did not recover renal function. Segmental necrotizing lesions are frequently present in IgAN; however, the small percentage of necrotizing lesions does not justify acute renal failure [5]. Thus, epithelial growth is not thought to play a significant role in macroscopic haematuria-associated AKI [5].

Warfarin coagulopathy may cause AKI in patients with underlying chronic kidney disease by inducing or exacerbating glomerular haematuria as observed in this patient [6]. Warfarin coagulopathy is often overlooked as a specific aetiological factor for AKI in haematuria. Oral anticoagulation and increased venous pressure may have contributed to intrarenal bleeding in our patient.

To our knowledge, this is the first report showing the presence of CD163-expressing macrophages in human renal interstitial haemorrhage and glomerular haematuria. Haemolysis of extravasated RBC releases Hb and leads to tissue accumulation of ferric ions (haemosiderin). Free Hb promotes the production of iron-derived hydroxyl radicals, inflammation and tissue injury. The plasma protein haptoglobin (Hp) protects from free Hb injury. Hp binds free Hb, and the Hp–Hb complex is exclusively cleared via CD163, a scavenger receptor on the surface of tissue macrophages [7]. A strong CD163 expression was observed in this patient’s renal tissue, suggesting a role of CD163 in the response to renal interstitial haemorrhage. Binding of CD163 to Hb induces anti-inflammatory pathways, increasing interleukin-10 release and HO-1 synthesis [8]. HO-1 attenuates the production of reactive oxygen species through degradation of heme [9,10]. HO-1 was previously associated with protection from AKI [10]. NADPH oxidase plays a key role in renal damage via production of superoxide. NADPH oxidase consists of several units, including p22 phox, which correlates with the amount of ROS and severity of AKI [9]. The elevated p22 phox and HO-1 localized to areas with interstitial haemorrhage, and RBC casts in this case illustrate the relationship between extravasated RBCs and oxidative stress. We hypothesize that anti-inflammatory responses by CD163-positive macrophages will contribute to restoration of tissue integrity and amelioration of renal function.

In conclusion, our patient has several predisposing factors for renal haemorrhage. Intrarenal haemorrhage was associated with local inflammation, oxidative stress and activation of protective mechanism. We hypothesize that oral anticoagulant could have favoured the bleeding in the congested renal tissue due to tricuspid insufficiency. RBC degradation products both promoted AKI and generated a compensatory protective response. Glomerular haemorrhage is not a benign condition, and anticoagulants should be stopped or decreased while macroscopic haematuria is present.

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