



EXCEPTIONAL CASE

Podocyte and tubular involvement in AngioJet-induced kidney injury

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ABSTRACT

The AngioJet technique combines localized thrombolysis and percutaneous mechanical thrombectomy (PMT). However, PMT may cause acute kidney injury (AKI), which has been ascribed to severe mechanical haemolysis, although no renal biopsies have been reported. We now report the first renal biopsy in a patient with AKI following PMT. There is histological evidence of haemoglobin (Hb)-induced tubular injury and podocyte stress characterized by intracellular Hb and staining for ferritin and hemo-oxygenase-1, suggestive of an adaptive response to oxidative stress. This confirms that Hb is involved in kidney cell injury and supports the existence of several different kidney cellular targets.

Keywords: acute kidney injury, AngioJet, haemoglobinuria, mechanical thrombolysis, podocyte, tubular cell

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INTRODUCTION

Percutaneous mechanical thrombectomy (PMT) using the AngioJet technique is used to treat arterial and deep vein thrombosis [1]. AngioJet combines a localized thrombolysis agent and PMT with a guided catheter that destroys and aspirates the thrombus. However, PMT may cause acute kidney injury (AKI), which has been ascribed to severe mechanical haemolysis, although no renal biopsies have been reported [2, 3]. We now report the first renal biopsy in post-PMT AKI and histological evidence of podocyte as well as tubular injury.

CASE REPORT

A 28-year-old man was diagnosed with right subclavian vein thrombosis following a trans-Atlantic flight. Despite oral anticoagulation, no improvement was observed and 2 weeks later he underwent AngioJet PMT. Six hours post-procedure he complained of dark brown urine and bilateral lumbar pain. Serum creatinine (sCr) was 2.9 mg/dL (baseline 1.0 mg/dL), platelets 240 000/ μ L, haemoglobin (Hb) 15 g/dL and lactate dehydrogenase (LDH) 3430 IU/L. He had dipstick haematuria +1 and proteinuria 70 mg/dL. Despite intravenous fluid (0.9% sodium chloride and 5% dextrose, 3000–5000 mL/day) and urine alkalinization, 5 days post-procedure (Supplementary data, Figure S1) his sCr was 9.78 mg/dL, Hb 11 g/dL, platelets 180 000/ μ L, LDH 1030 IU/L, indirect bilirubin 1.3 mg/dL and haptoglobin 5 mg/dL. Direct Coombs test was negative and no schistocytes were observed. Dipstick haematuria persisted, urinary protein:creatinine ratio was 731 mg/g and albuminuria was 191 mg/g. Prednisone 40 mg/24 h was started after renal biopsy.

The renal biopsy contained 20 glomeruli: these and the vessels in the biopsy appeared normal by light microscopy. Immunofluorescence for immunoglobulin G (IgG), IgA, IgM, C3 and light chains was negative. Severe diffuse acute tubular damage was characterized by tubular necrosis, occasional tubular basement membrane ruptures and adjacent interstitial inflammatory reaction (Figure 1A and B). Tubules were filled with abundant debris encompassing necrotic tubular cells, granular erythrocyte degeneration debris, isolated red blood cells and, in proximal tubules, eosinophilic filiform aggregates that stained for Hb (Figure 1B). Hb was observed in the cytoplasm of glomerular capillary endothelium, podocytes and tubular cells (Figure 2A and C). Tubular epithelial cells and podocytes stained for ferritin and hemo-oxygenase-1 (HO-1), suggestive of iron overload and an adaptive response to oxidative stress, respectively. The use of transmission electron microscopy showed mild podocyte damage, with foot process widening, large intracellular vacuoles and electron-dense iron deposits (Figure 2B). Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining confirmed the presence of dead intratubular cells (Figure 2D).

Ten days after the procedure, sCr peaked at 12 mg/dL while haemolysis was improving (haptoglobin 159 mg/dL, LDH 800 IU/L). Albuminuria was 288 mg/day and proteinuria was 900 mg/day 12 days after thrombectomy. sCr and urinalysis normalized 2 months after the procedure.

DISCUSSION

The incidence of AKI is higher following PMT than following catheter-guided thrombolysis without mechanical thrombectomy (20–29% versus 0–8%) [1, 3]. The average AKI duration was 5 days [1]. However, AKI may be severe enough to require

temporary dialysis (from 20 days to 5 months) [2, 3]. We present the first renal biopsy reported in this condition, which provided insights into the pathogenesis and involvement of different cell types. Circulating free Hb filters freely through the glomerular capillary wall and its toxicity to proximal tubular cells that uptake Hb is well characterized. Hb is reabsorbed by proximal tubules through the megalin/cubilin receptor complex, causing oxidative stress, mitochondrial damage and cell death, as well as the release of inflammatory cytokines, which would explain the tubular damage and the inflammatory infiltrate observed in our case. Additionally, Hb decreases nitric oxide availability and causes intratubular obstruction in the distal nephron.

Tubular cells have traditionally been considered the only cellular target of the adverse effects of Hb in the kidney. However, data from our group showed that podocytes are capable of capturing Hb, which alters their viability and functionality [4]. Thus Hb increases the production of reactive oxygen species and induces apoptosis in podocytes, as we have observed in cells in culture and experimental models of intravascular hemolysis. In addition, we described the presence of podocytes loaded with Hb in biopsies of patients with atypical haemolytic uremic syndrome (aHUS) and severe haemolysis [4]. Podocytes stained for Hb and ferritin, suggesting iron overload; phosphorylated pNrf2, a transcription factor driving antioxidant responses, and HO-1, an antioxidant enzyme that is part of the pNrf2-driven adaptive antioxidant response, were reported in patients with aHUS. These features support the concept of Hb-driven podocyte involvement in aHUS.

While albuminuria was not very severe in our patient, there is evidence from other nephropathies, such as childhood Fabry nephropathy, suggesting that histological evidence of podocyte injury (lysosomal accumulation followed by foot process widening followed by foot process effacement) precedes the development of pathological albuminuria and that a continuum of podocyte injury and resulting albuminuria exists [5]. aHUS is characterized by additional features, such as a local inflammatory response and local kidney and glomerular thrombotic microangiopathy. Therefore the results of the present case report represent a purer haemolysis model and confirms both the Hb-driven nature of AKI in AngioJet-induced AKI as well as the possible role of the podocyte as a new cellular target for the adverse effects of haemoglobinuria.

In conclusion, intravascular haemolysis secondary to mechanical thrombectomy due to AngioJet is associated with AKI characterized by acute tubular necrosis and podocyte involvement. This is the first histological description of AKI following this procedure.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj online](http://ckjonline.com).

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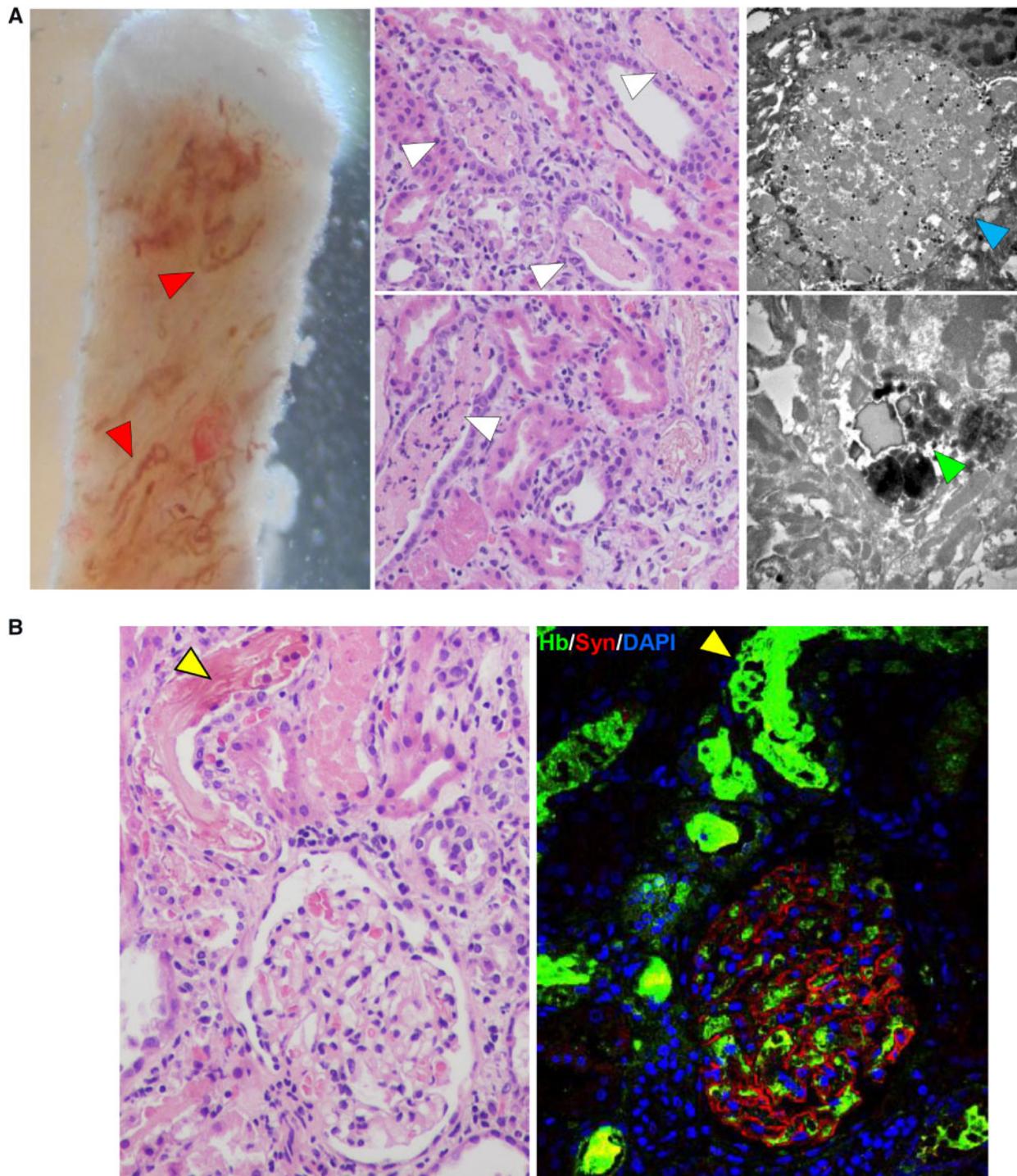


FIGURE 1: Characteristics of the renal biopsy. **(A)** A fresh renal biopsy specimen under a dissecting microscope (left; fresh $\times 40$) showing brownish and red casts that highlight the proximal tubules of renal cortex (red arrowheads), corresponding with microscopic evidence of foci of acute tubular necrosis, loss of brush border and intratubular contents composed of cell debris and protein [middle panel, haematoxylin and eosin (HE $\times 400$, white arrowheads)]. The right upper panel shows heterogeneous tubular casts with compact moderately electron dense areas, similar to erythrocyte cytoplasm, admixed with smaller and strongly electron dense material (blue arrowheads). The right lower panel shows a detail of electron dense material, showing a vaguely crystallized appearance, identified in the cytoplasm of some cortical tubules (green arrowheads). **(B)** The left panel shows an H&E image ($\times 400$) of a proximal tubule in its first portion filled with eosinophilic filiform content corresponding to free Hb filtered by the glomerulus (yellow arrowheads), as identified by specific immunostaining shown in the right panel for Hb (green). Additional staining was for podocytes [synaptopodin (Syn), red] and nuclei [4',6-diamidino-2-phenylindole (DAPI), blue], as determined by confocal microscopy.

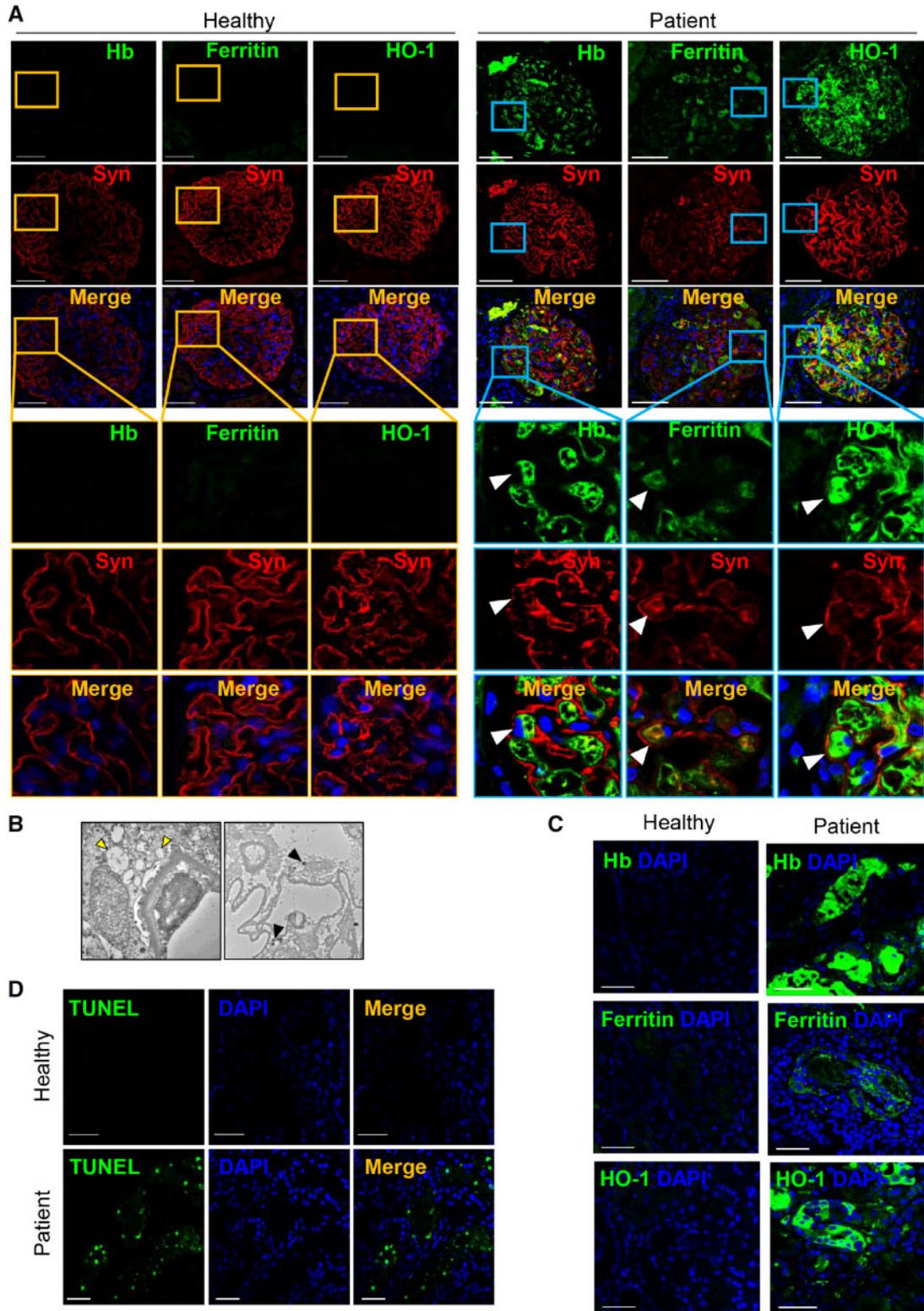


FIGURE 2: Glomerular and tubular immunostaining of the renal biopsy. (A) Representative confocal microscopy images showing co-localization (white arrowheads) of Hb (green), ferritin (green) and HO-1 (green) with the podocyte marker synaptopodin (Syn, red) in the renal biopsy of the patient with AKI haemolysis. Note that there was no staining in the control samples from non-tumour renal tissue after surgery in patients with kidney cancer. The rectangle shows the region of interest for which high-magnification images are shown in the lower panels. (B) Representative images of transmission electronic microscopy showing a high number of vacuoles (left panel, yellow arrowheads) and the presence of intensely electron dense and compact cytoplasmic inclusions (right panel, black arrowheads) in podocytes as well as foot process widening in the renal biopsy of the patient. (C) Localization of Hb (green), ferritin (green) and HO-1 (green) in tubular epithelium. (D) Representative confocal microscopy images showing the presence of dead intratubular cells (TUNEL-positive cells, green). Nuclei were stained with [4',6-diamidino-2-phenylindole (DAPI), blue]. Scale bars: 50 μ m.

CONFLICT OF INTEREST STATEMENT

None declared.

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