CASE REPORT

Acute renal injury in a patient with concomitant paroxysmal nocturnal hemoglobinuria, glucose-6-phosphate dehydrogenase deficiency and renal cell carcinoma

Kai-Po Chang[1], Wen-Chi Chen[2], Ching-Chan Lin[3], Han Chang[4]

1. Department of Pathology, China Medical University Hospital, Taichung, Taiwan. 2. Department of Urology, China Medical University Hospital; Graduate Institute of Integrated Medicine, China Medical University, Taichung, Taiwan. 3. Division of Hematology and Oncology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan. 4. Department of Pathology, School of Medicine, China Medical University; Department of Pathology, China Medical University Hospital, Taichung, Taiwan.

Correspondence: Han Chang. Address: 2 Yuh-Der Road, Taichung, Taiwan, 40447, R.O.C. E-mail: changhan@mail.cmu.edu.tw

Received: July 9, 2014 **Accepted:** August 22, 2014 **Online Published:** September 10, 2014
DOI: 10.5430/crcp.v2n1p23 **URL:** http://dx.doi.org/10.5430/crcp.v2n1p23

Abstract

The authors report a case of concomitant glucose-6-phosphate dehydrogenase (G6PD) deficiency, paroxysmal nocturnal hemoglobinuria (PNH) and renal cell carcinoma (RCC). The 53 year-old male had G6PD deficiency and accepted repeated blood transfusions due to episodes of hemolytic anemia. Unilateral nephrectomy was performed due to RCC. PNH diagnosed by flow cytometry showing CD24-deficient granulocytes with clonality of 99%, CD14-deficient monocytes with clonality of 94% and CD59-deficient red blood cells with clonality of 17%. Histopathology showed a clear cell RCC, acute tubular injury, and renal artery thrombosis. Hemosiderin deposition was prominent in damaged renal tubular cells. CD163 protein is a hemoglobin scavenger receptor. Mononuclear infiltrates, including CD163-expressing macrophages, appeared in the renal interstitium. CD133 is a marker for renal progenitor cells. Apical CD133 expression focally increased in cells of tubular regeneration and RCC. These imply hemoglobin toxicity linked with tubulointerstitial renal injury.

Key words

Acute renal injury, Glucose-6-phosphate dehydrogenase deficiency, Paroxysmal nocturnal hemoglobinuria, Renal cell carcinoma

1 Introduction

Paroxysmal nocturnal hemoglobinuria (PNH), a rare disease manifesting intravascular hemolysis and thrombosis, is caused by deficiency of CD55 and CD59 glycosylphosphatidylinositol-anchored proteins (GPI-APs) on cell membrane [1]. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect in Taiwan: 3% prevalence [2]. Persons afflicted may exhibit nonimmune hemolytic anemia in response to infection or exposure to oxidants. Renal injury in cases of PNH or other hemolytic anemia, such as G6PD deficiency, is common. Yet renal injury in those

with concomitant PNH and G6PD deficiency was not reported. Prior studies of renal injury in PNH suggest free hemoglobin (Hb) inducing oxidative cytotoxic to tubular epithelial and endothelial cells, culminating in renal tubular injury [3, 4]. A study aiming at renal cell carcinoma (RCC) mechanism showed similar molecular traits to tubular regeneration after renal injury [4]. We report a case of acute renal injury in a 53-year-old male with concomitant G6PD and PNH after unilateral nephrectomy due to RCC. Immunohistochemistry proved linkage between Hb and renal injury; current evidence was reviewed.

2 Case presentation

In May 1997, the 53-year-old male was first admitted, complaining of dizziness, general weakness, and dark urine for ten days. G6PD deficiency diagnosed during health examination and genetic counseling before marrying in 1995. He had a common cold, but no exposure to fava beans, sulfa drugs, or naphthalene. While hospitalized, his laboratory tests showed low serum hemoglobin (8.6 g/dl), with greater mean corpuscular volume (108 fl), and red cell distribution width (21.7%). Levels of blood urea nitrogen (BUN), creatinine, alanine (ALT), and aspartate trasaminases (AST) were within normal limits; total bilirubin (2.52 mg/dl) and lactate dehydrogenase (3154 IU/L) were increased; haptoglobin was undetectable (less than 0.243 g/L). The occult-blood test in urine was positive. Direct Coomb's test was negative. Indirect Coomb's test was positive. Splenomegaly was found by physical examination and computed tomography. Symptoms improved after splenectomy and blood transfusions.

During follow-ups (1997-2005), some severe hemolytic crises occurred in response to upper airway infections. G6PD level tallied 1.07 U/gHb (normal values 6.4-12.9 U/gHb) in 2004. There was no evidence of liver or renal dysfunction. Until in October 2006, severe hemolytic anemia recurred, concomitant with higher ALT/AST levels. Sonography showed acute cholecystitis caused by gall stones and left renal cyst. In November 2007, streptococcal pneumonia exacerbated his chronic hemolytic anemia and first transient renal dysfunction. Given evidence of repeated exacerbations of chronic calculous cholecystitis concomitant with hemolytic crises and abnormal liver enzymes, he received cholecystectomy in October 2010.

A multi-locular cyst in the left kidney was found incidentally by abdominal sonography in 2006. Since then, follow-up computed tomographies showed increasing size and enhancement in this renal cyst, impressed as a carcinoma in February 2014. Therefore, the patient accepted a left nephrectomy while suffering transient acute renal dysfunction. Long-term chronic hemolytic anemia and positive indirect Coomb's test, in addition to histopathology, meant G6PD deficiency concomitant with PNH or autoimmune hemolytic anemia suspected. Serology tested negative for anti-cardiolipin IgG and IgM. Flow cytometry showed GPI-AP-deficient cells in three hematologic lineages: CD14-deficient monocytes by 93.79%, CD24-deficient granulocytes by 99.66%, and CD59-deficient red blood cells by 17.28%; these averred G6PD deficiency and PNH. Regular follow-ups were conducted in clinic.

Pathological findings

Grossly, resected kidney was black and heavy, with a renal cystic tumor measuring 3.0 cm × 2.5 cm × 2.5 cm located at the upper part of the kidney. Microscopically, left renal cystic tumor was a clear-cell RCC (see Figure 1). Also, areas of tubular injury exhibited focal epithelial necrosis, sloughing of apical plasma membranes alongside vacuolization of the cytoplasm (see Figure 2a), and fluid retention within tubular lumens. Iron stain demonstrated prominent iron or hemosiderin depositions in renal tubular cells (see Figure 2b). CD163 protein is a hemoglobin scavenger receptor. Mononuclear cell infiltrates, including CD163-expressing macrophage, were evident in the renal interstitium (see Figure 2c). CD133 protein is a marker for renal progenitor cells of the parietal epithelial layer of Bowman's capsule. Area of tubular regeneration featured nuclear prominence and flattening of tubular cells, where apical CD133 expression increased (see Figure 3a). Apical CD133 also was focally expressed in RCC cells (see Figure 3b). Thrombosis was found in renal artery.

 ISSN 2331-2726 E-ISSN 2331-2734

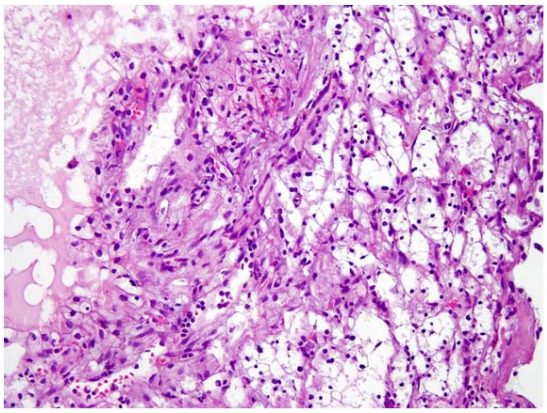

Figure 1. Clear cell renal cell carcinoma (H&E, 200×)

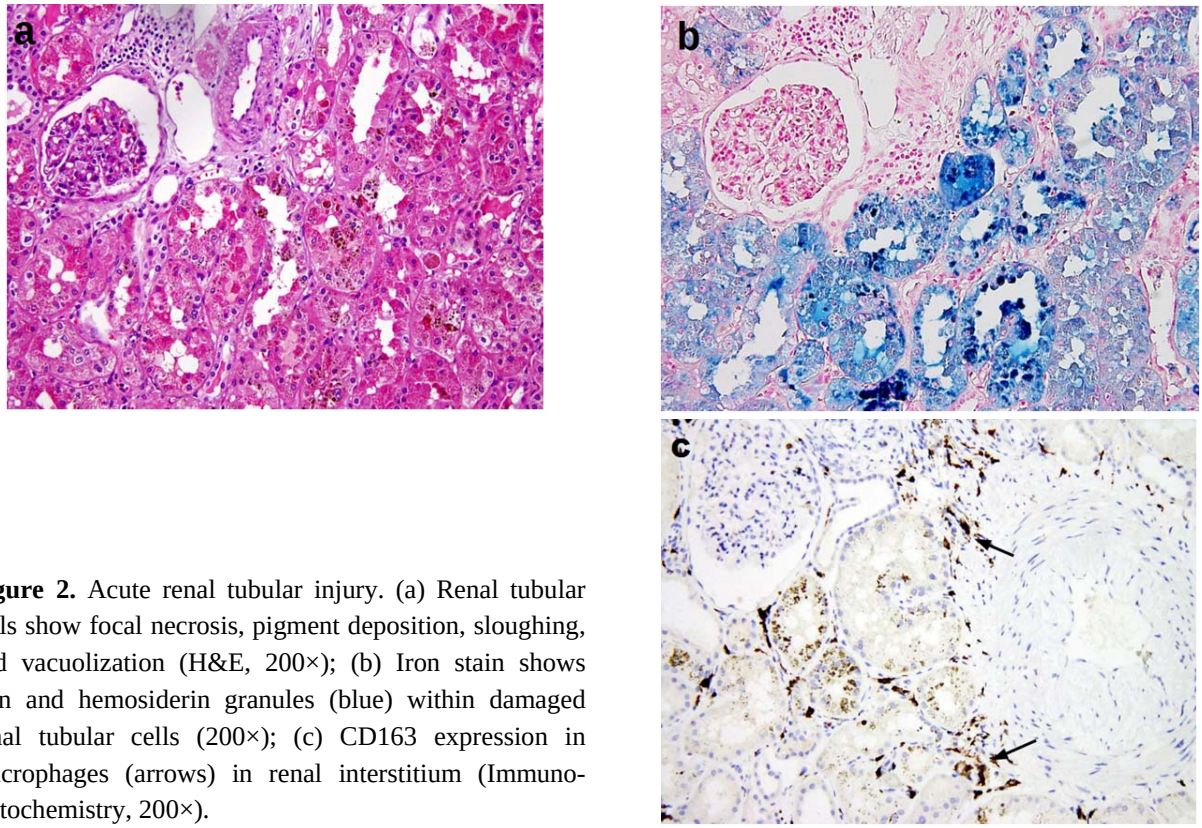

Figure 2. Acute renal tubular injury. (a) Renal tubular cells show focal necrosis, pigment deposition, sloughing, and vacuolization (H&E, 200×); (b) Iron stain shows iron and hemosiderin granules (blue) within damaged renal tubular cells (200×); (c) CD163 expression in macrophages (arrows) in renal interstitium (Immunohistochemistry, 200×).

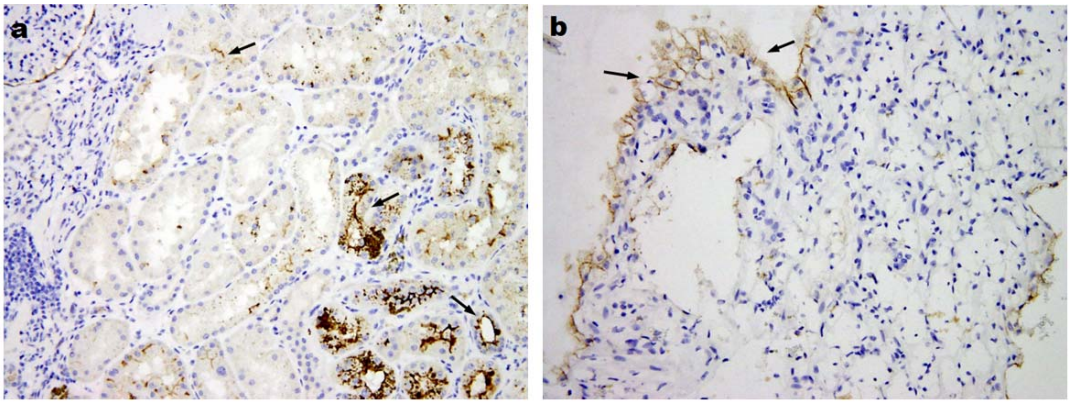

Figure 3. CD133 immunohistochemistry. Apical positivity (arrows) in regenerative or damaged renal tubular cells (a, 200×) and focal in renal cell carcinoma (b, 200×).

3 Discussion

Free Hb or heme can cause cytotoxic effects induced by reactive oxygen species (ROS) formation, apoptosis and inflammation in cell and animal models [3, 5, 6]. One in-vitro study by Schaer (2006) proved that when free Hb treated macrophages, those with Hb scavenger receptors (CD163) could bind and uptake Hb while inducing anti-inflammatory and cytoprotective gene expression: *e.g.*, heme oxygenase (HO-1) [7]. In a reported PNH case, renal tissue showed tubular injury with hemosiderin accumulation and CD163/HO-1-coexpressing macrophages in the interstitium [8]. In the present case with concomitant PNH and G6PD deficiency, tubular cells and interstitium displayed hemosiderin deposition, with CD163-positive macrophages near areas where lining tubules contained iron deposition. These portended Hb-induced renal tubular injury and interstitial fibrosis, with CD163 may play a non-inflammatory Hb scavenger role in the Hb-induced tubulointerstitial injury.

Earlier studies hinted correlation between RCC and chronic renal injury with regeneration/repair [4, 9-12]. An animal study focused on pathogenesis-related genes encoded as hypoxia-inducible factors, Von Hippel-Lindau tumor suppressor, insulin-like growth factors, Myc and mitogenic signals, or nuclear factor kappa-light-chain-enhancer of activated B cells [4], in which 77% of studied genes exhibited similar expression patterns between renal cell regeneration/repair and carcinoma in mice [4]. Kidney injury molecule-1 expression arose in damaged proximal tubules and human RCC [9]. Free iron can induce oxidative stress by activating ROS, and this stimulation may be carcinogenic, as cited in a review [10]. Clinical evidence indicated higher RCC incidence in patients receiving long-term dialysis [11, 12]. Additionally, Bussolati (2008) showed CD105-positive (CD105+) and CD133-positive (CD133+) cells isolated from human clear cell RCC by flow cytometry, then injected into mice [13]. Only mice with CD105+-cell injection had RCC growth; CD133+-cell injection spawned vascular proliferation rather than tumor formation [13]. Bruno's study (2006) gleaned similar findings that suggest CD133+ cells as not tumor stem cells, but a progenitor for angiogenesis [14]. In the present case, CD133+ cells focally increased in areas of regenerative renal tubules and RCC. Therefore, CD133+ cells probably indirectly take part in renal tubular regeneration and tumor growth, including RCC.

4 Conclusions

The case with concomitant PNH, G6PD deficiency and RCC is the first reported. Since G6PD deficiency is the most common human enzyme defect, coexistence of G6PD deficiency with other hemolytic anemia is necessary to keep in differential diagnoses when patients manifest unusual hemolytic crises. Presence of CD163-expressing macrophages implies Hb toxicity involved in tubulointerstitial renal injury. CD133-expressing cells may play a role in such pathology.

References

[1] Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, *et al*. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106(12): 3699-3709. http://dx.doi.org/10.1182/blood-2005-04-1717

[2] Chang JG, Chiou SS, Perng LI, Chen TC, Liu TC, Lee LS, *et al*. Molecular characterization of glucose-6-phosphate dehydrogenase (G6PD) deficiency by natural and amplification created restriction sites: five mutations account for most G6PD deficiency cases in Taiwan. Blood. 1992; 80(4): 1079-1082. PMid: 1323345.

[3] Nath KA, Balla J, Croatt AJ, Vercellotti GM. Heme protein-mediated renal injury: a protective role for 21-aminosteroids in vitro and in vivo. Kidney Int. 1995; 47(2): 592-602. http://dx.doi.org/10.1038/ki.1995.75

[4] Riss J, Khanna C, Koo S, Chandramouli GV, Yang HH, Hu Y, *et al*. Cancers as wounds that do not heal: differences and similarities between renal regeneration/repair and renal cell carcinoma. Cancer Res. 2006; 66(14): 7216-7224. http://dx.doi.org/10.1158/0008-5472.CAN-06-0040

[5] Reeder BJ, Svistunenko DA, Wilson MT. Lipid binding to cytoglobin leads to a change in heme co-ordination: a role for cytoglobin in lipid signaling of oxidative stress. Biochem J. 2011; 434(3): 483-492. http://dx.doi.org/10.1042/BJ20101136

[6] Goldman DW, Breyer RJ, Yeh D, Brockner-Ryan BA, Alayash, AI. Acellular hemoglobin- mediated oxidative stress toward endothelium: a role for ferryl iron. Am J Physiol. 1998; 275(3 Pt 2): H1046-1053. PMid: 9724312.

[7] Schaer CA, Schoedon G, Imhof A, Kurrer MO, Schaer DJ. Constitutive endocytosis of CD163 mediates hemoglobin-heme uptake and determines the noninflammatory and protective transcriptional response of macrophages to hemoglobin. Circ Res. 2006; 99(9): 943-950. http://dx.doi.org/10.1161/01.RES.0000247067.34173.1b

[8] Ballarin J, Arce Y, Torra Balcells R, Diaz Encarnacion M, Manzarbeitia F, Ortiz A, *et al*. Acute renal failure associated to paroxysmal nocturnal haemoglobinuria leads to intratubular haemosiderin accumulation and CD163 expression. Nephrol Dial Transplant. 2011; 26(10): 3408-3411. http://dx.doi.org/10.1093/ndt/gfr391

[9] Han WK, Alinani A, Wu CL, Michaelson D, Loda M, McGovern FJ, *et al*. Human kidney injury molecule-1 is a tissue and urinary tumor marker of renal cell carcinoma. J Am Soc Nephrol. 2005; 16(4): 1126-1134. http://dx.doi.org/10.1681/ASN.2004070530

[10] Toyokuni S. Role of iron in carcinogenesis: cancer as a ferrotoxic disease. Cancer Sci. 2009; 100(1): 9-16. http://dx.doi.org/10.1111/j.1349-7006.2008.01001.x

[11] Bretan PN, Busch MP, Hricak H, Williams RD. Chronic renal failure: a significant risk factor in the development of acquired renal cysts and renal cell carcinoma. Case reports and review of the literature. Cancer. 1986; 57(9): 1871-1879. http://dx.doi.org/10.1002/1097-0142(19860501)57:9<1871::AID-CNCR2820570929>3.0.CO;2-3

[12] Kojima Y, Takahara S, Miyake O, Nonomura N, Morimoto A, Mori H. Renal cell carcinoma in dialysis patients: a single center experience. Int J Urol. 2006; 13(8): 1045-1048. http://dx.doi.org/10.1111/j.1442-2042.2006.01498.x

[13] Bussolati B, Bruno S, Grange C, Ferrando U, Camussi G. Identification of a tumor-initiating stem cell population in human renal carcinomas. FASEB J. 2008; 22(10): 3696-3705. http://dx.doi.org/10.1096/fj.08-102590

[14] Bruno S, Bussolati B, Grange C, Collino F, Graziano ME, Ferrando U, *et al*. CD133+ renal progenitor cells contribute to tumor angiogenesis. Am J Pathol. 2006; 169(6): 2223-2235. PMid: 17148683. http://dx.doi.org/10.2353%2Fajpath.2006.060498.