Abstract:
AN INTERESTING CASE OF PIGMENT INDUCED ACUTE KIDNEY INJURY

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal disorder associated with somatic mutations of the X-linked phosphatidylinositol glycan anchor biosynthesis class A gene in hematopoietic stem cells, which results in the absence of the phosphatidylinositol-linked proteins necessary to protect cells from complement-mediated lysis. The primary clinical manifestations of PNH include intravascular haemolytic anaemia, thrombosis in vessels and bone marrow failure, which can cause pancytopenia. Reversible acute kidney injury (AKI) due to haemolysis-induced severe tubular damage is a recognized complication of paroxysmal nocturnal haemoglobinuria (PNH). It has been proposed that acute tubular necrosis and AKI associated with PNH results from tubular haemoglobin (Hb)-mediated toxicity due to haemolysis. We report a case of AKI associated to haemolysis. We report a case of AKI associated to PNH and extensive haemosiderin deposits in tubular cells which gave a positive reaction on Perl's stain, consistent with deposition of ferric ions (haemosiderin). Patient was managed with intravenous fluids and on second day, there was normalization of serum creatinine. On follow-up patient continues to have normal serum creatinine.

Keyword:
paroxysmal nocturnal haemoglobinuria, phosphatidylinositol glycan, haemosiderin, acute kidney injury, clonal disorder, haemosiderin, hemolysis

INTRODUCTION:
Reversible AKI due to haemolysis-induced severe tubular damage is a recognized complication of paroxysmal nocturnal haemoglobinuria (PNH). It has been proposed that acute tubular necrosis and AKI associated with PNH.
results from tubular haemoglobin (Hb)-mediated toxicity due to haemolysis [1]. However, there is little information on the mechanisms via which Hb promotes renal damage in PNH from human renal biopsies. We now show a case of AKI associated with PNH with haemosiderin deposition in renal tubules.

**CASE REPORT:**
A 48-year-old man was referred to our hospital in July 2010 because of passing cola colored urine (January 2010 to July 2010). during early morning, reduced in intensity over the day, preceded by loin pain (fig.1). He had a history of fever and renal failure, recovered spontaneously (Oct 2006). At presentation, he was anemic and normotensive. Urine examination revealed moderate proteinuria and macroscopic haematuria, 24 hour urine protein was 1.8g/day. Blood investigations revealed haemoglobin 8.5 g/dL, peripheral blood smear showed macrocytic anaemia, fasting blood sugar was 180mg/dl, postprandial blood sugar was 232mg/dl, serum creatinine was 2.4mg/dl. Elevated levels of Reticulocyte (12.2 %) and LDH (3362 U/L) were observed. Direct Coombs test was negative. HbF – 5.49% (Adult <1%), MCV- 116.2H, Increased MCV and elevated HbF might be indicative of folic acid deficiency. Bone marrow biopsy showed megaloblastic changes. Abdominal ultrasonographic examination showed normal-sized kidneys with normal echogenicity and corticomedullary differentiation. Light microscopy of the kidney biopsy revealed 12 unremarkable glomeruli. Light microscopy of the kidney biopsy revealed 12 unremarkable glomeruli. The tubules showed diffuse deposition of brown-coloured pigment, which gave a positive on Perl's stain, consistent with deposition of ferric ions (haemosiderin) (Figure 2,3). There were structural changes indicative of tubular damage, such as dis- tention of tubules and cell debris in the lumina. There was neither interstitial fibrosis nor vascular changes. Immunofluorescence was negative. Following renal biopsy report we did flow cytometry that showed the patient's granulocytes were found to be deficient in CD59, CD55 and CD58 with a clonality of 58.5 %, 23.6 %, 94.9 % respectively. In addition, 50% of the erythrocytes were deficient in CD59, CD55 and CD58, showing a similar clone. A diagnosis of PNH was therefore made. Treatment with intravenous fluids, oral folinic acid 5mg BD was started. The dark colour of the urine disappeared progressively and there was a rapid and clear improvement in haematologic values and serum creatinine declined to 1.0mg/dl over the next 2 days.

**DISCUSSION:**
PNH is an acquired clonal disorder associated with somatic mutations of the X-linked phosphatidylinositol glycan anchor biosynthesis class A gene in hematopoietic stem cells, which results in the absence of the phosphatidylinositol-linked proteins necessary to protect cells from complement-mediated lysis [2]. The primary clinical manifestations of PNH include intravascular haemolytic anaemia, thrombosis in vessels and bone marrow failure, which can cause pancytopenia. Renal involvement in PNH is usually not clinically apparent but essentially all patients with classic PNH report gross haemoglobinuria at some point during the course of their illness. However, when renal disease is significant, it usually manifests as AKI and rarely as chronic kidney disease (CKD) [3]. Treatment of PNH has been largely symptomatic but as the haemolysis of PNH is a consequence of complement mediated cytolysis, inhibition of complement is a logical approach to therapy. Eculizumab is a humanized monoclonal antibody that targets com
humanized monoclonal antibody that targets complement protein C5, thereby preventing production of the pro-inflammatory mediator C5a and the assembly of the membrane attack complex. Data from treated patients demonstrated a reduction in haemolysis and a reduction in thrombotic events. Administered to patients with renal dysfunction was well tolerated and usually associated with clinical improvement [4, 5]. In certain cases of severe haemolysis as in the case of our patient, the concentration of haemoglobin in the tubular filtrate becomes sufficiently high to impair renal function and AKI results. In these patients, conservative treatment, which includes fluid administration and urine alkalization, improves renal function [3, 6, 7]. Corticosteroids, attenuating acute haemolytic exacerbations, may reduce the severity and duration of the crisis[8]. However, their efficacy is limited and is not recommended for long-term treatment. Reversible AKI in PNH is thought to depend on renal epithelial haemoglobin-mediated toxicity due to haemolysis, contraction of renal blood vessels and intratubular obstruction [6, 7]. Intravascular haemolysis releases Hb into plasma, where Hb is bound quickly to haptoglobin (Hp), forming a Hp–Hb complex[8]. Under normal conditions, this large complex is not filtered by glomerulus and is further degraded by the liver, spleen and bone marrow and degraded. In persistent intravascular haemolysis, plasma haptoglobin is consumed and free Hb accumulates in plasma and dissociates from its usual tetrameric form to dimeric Hb. Dimeric Hb is filtered more easily by the glomerulus and incorporated into proximal tubules, leading to accumulation of ferric ions (haemosiderin) in these cells [8]. The renal biopsy showed haemosiderin deposits in tubular cells, most prominent in the proximal tubules. Although haemosiderin accumulates quite rapidly in tubules, its role in AKI remains controversial since intense renal haemosiderosis can be found in PNH patients with normal renal function [6].

CONCLUSION:
In patients with AKI where there is suggestion of hemolysis, it is pertinent to look for underlying hemolytic disorders. We report a patient who has PNH which was associated with tubular haemosiderin deposits and caused AKI.
References:


