CASE REPORT

Acute kidney injury in a diabetic haemophiliac: one step at a time

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SUMMARY

We present a young man with type 1 diabetes mellitus and haemophilia A; who presented with oliguric acute kidney injury (AKI). He is also known to have chronic hepatitis C virus infection. On presentation, he had an active urinary sediment warranting a renal biopsy for definitive diagnosis and management. Although he was at high risk for bleeding we elected for renal biopsy with appropriate factor VIII supplementation and monitoring. Ultrasound-guided percutaneous renal biopsy was successful with no immediate or long-term complications. Biopsy revealed advanced diabetic glomerulosclerosis with mild chronic interstitial inflammation.

BACKGROUND

Diabetic kidney disease is the leading cause of end-stage renal disease (ESRD) in adults. The duration of type 1 diabetes and the magnitude of glomerular pathology are not clearcut. Some patients may develop ESRD after a duration of 15 years while others maintain renal function for decades. Haemophilia A is the most common X-linked inherited bleeding disorder. Urinary tract bleeding is the second most common manifestation after hemarthrosis in haemophiliacs.¹ There is no specific glomerulopathy in patients with haemophilia A and they often have benign haematuria, majority of the time renal involvement is secondary to bleeding and clot formation in the urinary tract.^{2,3} Our patient had type 1 diabetes mellitus, haemophilia A and chronic hepatitis C viral infection, all broadening the differential diagnosis for acute kidney injury (AKI). Additionally, we performed a high-risk renal biopsy without complications.

CASE PRESENTATION

A 33-year-old man presented to the emergency room with a 1 week history of right knee swelling and pain with no history of trauma. He also presented with lower abdominal discomfort and noticed a decrease in urine output, facial puffiness and bilateral lower limb swelling for the same duration. History was negative for associated fever, chills or rigours. He denied any new medication use. He denied any change in the colour of urine and had no systemic symptoms. His medical history is significant for haemophilia A treated with recombinant factor VIII. He has had multiple admissions for recurrent hemarthrosis and infectious arthritis that was conservatively managed. Nine months ago he had completed a 60 day course of amoxicillin/

clavulanic acid for osteomyelitis of the left knee. He suffers from type 1 diabetes mellitus treated with insulin for the last 18 years. His diabetes is complicated with diabetic retinopathy and maculopathy status-post intravitreal bevacizumab and pan-retinal photocoagulation of both eyes 6 months ago. He presented with frequent episodes of hypoglycaemia over the past few months with no change in insulin doses. He is known to have chronic hepatitis C viral infection diagnosed in 2005, and is status-post treatment achieving sustained viral and biochemical response. Status-post appendectomy in 2007, forearm bleeding and compartment syndrome status-post fasciotomy in 2004. Dental extraction complicated with facial haematoma that was conservatively managed in 2003. His current medications are antihemophilic factor 2000 units subcutaneously three times weekly, vitamin D₃ 1000 units daily, mixtard 30 insulin 20 units two times a day, acetaminophen and ibuprofen occasionally for joint pain. He is single and works as a nurse. On physical examination, he was underweight with a body mass index of 15.8 kg/m². His blood pressure was 172/99 mm Hg, pulse 98/min, with a respiratory rate of 18/min saturating at 100% on room air and afebrile. He was conscious, oriented and alert in mild distress. He had puffy eye lids, no pallor, icterus or lymphadenopathy. There were no visible skin rashes, mucosal or cutaneous evidence of bleeding. Examination of the chest revealed fine bibasal crepitations. The abdomen was soft and lax with a visible and palpable tender mass in the lower abdomen which was a distended urinary bladder. There were no other masses or organomegaly. There was +2 pitting oedema of the lower limbs bilaterally with right knee swelling that was mildly tender but not warm or erythematous. He had asymmetry of his knee joints, Charcot arthropathy of left ankle with diminished sensation of both upper and lower extremities in a glove and stocking distribution.

INVESTIGATIONS

On presentation serum creatinine was 250 µmol/L; his baseline serum creatinine was 86 µmol/L with an estimated-glomerular filtration rate (eGFR) >60 measured 8 months earlier. Urinalysis showed +2 protein, +2 glucose and 6–10 red blood cells per high-power field. Bedside ultrasound of the urinary system revealed a distended bladder (figure 1), echogenic kidneys with a dilated pelvicalyceal system; the right kidney measured 10.95 cm and the left kidney measured 10.84 cm (figure 2). Twenty-four hour proteinuria was 6 g with a serum albumin level

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Figure 1 Ultrasound showing a distended urinary bladder.

of 24.9 g/L. Coagulation profile revealed PT 13.5 s, partial thromboplastin time of 48 s, international normalised ratio was 1.1 and factor VIII activity was 1.68 IU/mL (0.5–2.0). Anti-factor VIII inhibitor was undetectable. C reactive protein was 25.2 mg/L, intact parathyroid hormone was 288 ng/L and the glycated haemoglobin was 6.8%. Blood count revealed a haemoglobin level of 82 g/L with white cell count and platelets within normal range. Serology revealed that he was immunised for hepatitis B virus. Hepatitis C virus (HCV) antibodies were reactive but HCV RNA was undetectable by PCR. HCV genotype was 3a, cryoglobulin was previously present; however it was currently absent after treatment. HIV 1 and 2 antibodies were negative.

DIFFERENTIAL DIAGNOSIS

- ▶ AKI secondary to urinary retention secondary to diabetic cystopathy
- ▶ Postrenal obstruction secondary to bleeding and clot formation in the urinary tract
- ▶ Postinfectious glomerulonephritis
- ▶ Hepatitis C virus-related nephropathy:
 - Membranoproliferative glomerulonephritis (MPGN) in the setting of cryoglobulinemia
 - Membranous nephropathy (MN)
 - Polyarteritis nodosa (PAN)
 - Focal segmental glomerulosclerosis (FSGS)
 - IgA nephropathy
 - Immunotactoid glomerulopathy
 - Fibrillary glomerulonephritis
- ▶ Diabetic kidney disease
- ▶ Chronic tubulointerstitial nephritis secondary to repeated antibiotic use
- ▶ Non-steroidal anti-inflammatory drug (NSAID)-induced nephropathy

Figure 2 Renal ultrasound showing echogenic kidneys with pelvicalyceal dilation.

TREATMENT

Based on the ultrasound findings our top differential was AKI secondary to urinary retention secondary to diabetic cystopathy. Our management included inserting a foley catheter, avoided excessive intravenous hydration to avoid postobstructive diuresis, daily renal profile, strict charting of intake and output as well as daily weight.

OUTCOME AND FOLLOW-UP

The patient had adequate urine output and became euvolaemic within 24 h of inserting the foley catheter; the expected clinical course is gradual improvement of serum creatinine. However this was not the case, serum creatinine was persistently elevated (figure 3). Our extended differential diagnosis is listed above. At this point we investigated further; complement C3 was 0.88 g/L (0.9–1.8) and C4 was 0.24 g/L (0.1–0.4). Antinuclear antibody, cytoplasmic antineutrophil cytoplasmic autoantibody (C-ANCA), perinuclear antineutrophil cytoplasmic autoantibody (P-ANCA), ANCA immunofluorescence and antiglomerular basement membrane antibody (anti-GBM) were all negative. We suspected that given the duration of diabetes, the natural progression from microalbuminuria to overt proteinuria and the presence of diabetic retinopathy, the patient most likely had diabetic kidney disease (DKD). Additionally a clue to progressive DKD was the decreasing need for insulin due to lower insulin clearance. The acute rise in serum creatinine that did not resolve when the obstruction was relieved discounts diabetic cystopathy as the only cause of renal impairment. In the setting of an active urinary sediment, the history of HCV infection, recurrent antibiotic and NSAID use, we had to rule out a coexisting glomerulopathy that may be treatable. However, performing a renal biopsy in a haemophiliac is not without risk. There are reported cases where percutaneous liver biopsies were successfully performed in haemophiliacs.^{4–6} A report of the first renal biopsy performed in a patient with haemophilia A⁷ followed the same protocol as they did for the liver patients in previous studies^{6,8} where they administered recombinant factor VIII at a dose of 50–60 units per kilogram (Kg) body weight in the evening and in the morning and evening the day after while monitoring factor VIII activity, the renal biopsy revealed cryoglobulinaemic membranoproliferative glomerulonephritis associated with hepatitis C and the patient was treated with a favourable outcome.⁷ We elected to perform an ultrasound-guided percutaneous renal biopsy for a definitive tissue diagnosis to direct management in this young patient with renal impairment. We followed the same protocol for factor VIII administration as performed previously and the renal biopsy was performed using an 18-gauge needle. The patient tolerated the procedure well with no immediate or late complications. The kidney biopsy under light microscopy revealed 18 of the 41 glomeruli that were globally sclerosed. The remaining viable glomeruli show moderate mesangial

Figure 3 Graph illustrating the change in creatinine from baseline to latest follow-up.

matrix expansion and hypercellularity with thickening of the capillary walls and patent capillary lumina. Seven glomeruli showed mesangial nodule formation (Kimmelstiel-Wilson nodule). There was moderate interstitial fibrosis and tubular atrophy (30–40% of the cortical tissue), associated with mild interstitial inflammation composed mainly of lymphocytes. Arteries were unremarkable. Arterioles revealed mild subintimal hyalinosis (figure 4). Immunofluorescence revealed minimal mesangial staining for IgA. There was no significant glomerular staining with antisera specific for IgG, IgM, C3, C1q, Fibrinogen and κ and λ light chains. No extraglomerular staining was seen. Electron microscopy revealed peripheral capillary walls with diffuse irregular thickening. Mesangial areas showed increased mesangial matrix and hyalinosis. No electron dense deposits were seen. The podocytes show focal foot process effacement (30–40%) (figure 5). In conclusion, the nodular and diffuse mesangial sclerosis seen in the biopsy are consistent with

Figure 4 (Light microscopy) This glomerulus shows diffuse and nodular mesangial matrix expansion in addition to hypercellularity with thickening of the capillary walls and patent capillary lumina. Arteriolar hyalinosis is also seen (periodic acid-Schiff stain, $\times 400$).

diabetic nephrosclerosis. Other lesions were ruled out and the patient was managed with an ACE inhibitor for blood pressure control and minimising proteinuria, a statin, vitamin D supplementation and an erythrocyte-stimulating agent for his anaemia. Management of diabetic cystopathy was with intermittent self-catheterisation.

DISCUSSION

In a 3-year survey of adult persons with haemophilia (PWH), one of the most striking findings was a 50-fold increased risk of death as a result of renal disease compared with the general population.⁹ Risk factors for both AKI and CKD in PWH are HIV infection and hypertension; additionally kidney bleeding is a major risk factor for CKD. While haematuria is usually benign, idiopathic and often transient in younger PWH, for older PWH it may be associated with CKD.³ When HIV infection is present the cause of renal impairment may be HIV-associated nephropathy or immune complex glomerulonephritis; moreover, the nephrotoxicity associated with highly

Figure 5 (Electron microscopy) Increase in mesangial matrix with glomerular basement thickening.

active antiretroviral therapy and coinfection with HCV may also contribute to renal disease in these patients.^{10 11} Hypertension is more prevalent in PWH compared with the general population and is an independent risk factor for renal disease and may lead to renal bleeding.^{3 12} The presence of anti-factor VIII inhibitor may be linked to AKI; however, the pathogenesis is not clear.³ For PWH, screening and medical management of CKD is not different from that of the general population. When renal replacement therapy is entailed; haemodialysis, peritoneal dialysis and renal transplantation are all viable options.¹³

HCV infection is the main cause of chronic liver disease in PWH that may progress to end-stage liver disease (ESLD) necessitating liver transplantation; it remains the leading cause of death in this subpopulation.^{14–16} A staggering 98% of PWH treated with plasma-derived clotting factor concentrates before 1985 were infected with HCV, and in the majority, this has led to chronic liver disease.¹⁵ Concomitant HIV infection is a unique problem affecting more than half of PWH with HCV. Interestingly, HRs for progression to ESLD are as high as 8–14 in HIV-positive when compared with HIV-negative patients.^{17 18} Kidney injury due to HCV is mediated by cryoglobulins in the entity termed HCV-induced mixed cryoglobulinaemia. Cryoglobulins are deposited in the mesangium and their nephrotoxicity is related to a special affinity of the IgM-k rheumatoid factor for cellular fibronectin present in the mesangial matrix.^{19 20} The typical histopathological lesion of cryoglobulinaemic glomerulonephritis is MPGN.²¹ This pattern of injury is detected in around 80% of patients with HCV-associated type II mixed cryoglobulinaemia and glomerular involvement.²² Clinically, it manifests as nephritic syndrome. Several other glomerulonephritides can present with HCV infection as outlined in the differential diagnosis. Treatment is in the form of antiviral therapy driven by the theory that the underlying infection stimulates the formation of immune complexes and subsequent vasculitis. Recently, B cell depletion therapy with rituximab targeting B cells that produce cryoglobulins has been tried; however, this option is reserved for patients that are resistant or intolerant of antiviral therapy.²³

Many PWH are overweight and sedentary secondary to severe arthropathy as a result of recurrent haemarthrosis which accounts for more than 90% of all bleeding events.²⁴ This factor along with greater survivorship, older PWH are particularly vulnerable to the metabolic syndrome and diabetes mellitus (DM).¹³ In the general population, DM remains the most common cause of ESRD requiring dialysis and up to 44% of patients newly diagnosed with ESRD also carry a diagnosis of diabetes.²⁵ DKD is one of the most important long-term complications of DM and develops in 30–40% of patients with diabetes.²⁶ The clinical diagnosis of DKD usually depends on the presence of microalbuminuria (albumin excretion of more than 30 mg/g of creatinine in 2 out of 3 random urine samples collected within a 6-month period).²⁷ A proportion of patients with microalbuminuria will develop advanced DKD; referred to as overt nephropathy, clinical nephropathy, proteinuria or microalbuminuria.²⁸ Once microalbuminuria is confirmed, patients should undergo complete work-up for other possible aetiologies as other glomerulonephritides have been reported to coexist with DKD. DKD usually develops 10 years after the onset of type 1 DM, however with type 2 DM it is variable.^{29 30} Currently, there are no standardised criteria for kidney biopsy in patients with DM, but clinical presentation and progression can aid in making this decision. These are namely rapid onset of proteinuria regardless of progression from microalbuminuria to macroalbuminuria, absence of retinopathy, presence of an active

urinary sediment, rapid decline of renal function, unexplained renal failure on presentation and the presence of signs or symptoms of other systemic disease.³¹

In conclusion, although the risk of bleeding was high in our patient we opted for a renal biopsy in a case where DKD was most probable based on the fact that another glomerulopathy may coexist. Doing so he was spared from exposure to toxic medications currently indicated for lesions such as MPGN or MN. However, he now fits the criteria for chronic kidney disease (CKD) that is progressive. CKD is a worldwide public health problem and is characterised by kidney damage for greater than 3 months, defined by structural or functional abnormalities of the kidney, with or without decreased eGFR or GFR <60 mL/min/1.73 m².³¹ Currently, there is a worldwide rise in the number of patients with CKD reflected by the ever increasing population of patients with ESRD treated with renal replacement therapy.³² However, the number of patients with ESRD probably underestimates the entire burden of CKD because the numbers with earlier stages of CKD are likely to exceed by as much as 50 times those reaching ESRD.³³ Awareness of CKD among general practitioners is mandated for timely referral to a nephrologist for appropriate management.

Learning points

- ▶ A renal biopsy is indicated when retinopathy is not present in type 1 diabetes with proteinuria or moderately impaired renal function (absence of retinopathy does not exclude diabetic kidney disease (DKD) in type 2 diabetes).³¹
- ▶ Exclusion criteria for DKD include rapidly declining renal function, rapidly progressing proteinuria, an active urinary sediment, signs or symptoms of other systemic disease, refractory hypertension or greater than 30% decline in glomerular filtration rate from baseline after introducing an ACE inhibitor or an angiotensin receptor blocker.³¹
- ▶ An ultrasound-guided percutaneous renal biopsy can be safely carried out in a patient with haemophilia A following adequate factor VIII supplementation and monitoring.

Competing interests None.

Patient consent Obtained.

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