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Case Report

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An unusual cause of acute renal failure in sickle cell disease

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Abstract

A young female with sickle cell disease was treated for biopsy-proven IgA nephropathy. Serum creatinine levels resolved to normal range, but a year later, she presented with oedema, hypertension and acute renal failure. A repeat renal biopsy showed acute-on-chronic thrombotic microangiopathy (TMA). We suggest that circulating microparticles could be a pathophysiological link between sickle cell disease and the development of renal TMA. This case emphasizes the importance of a further biopsy for acutely declining renal function, even when a definite diagnosis has been made from a previous biopsy.

Keywords: acute renal failure; renal pathology; sickle cell disease; thrombotic microangiopathy

Background

In sickle cell disease, a single amino-acid substitution causes sickling of deoxygenated red blood cells (RBCs) and the development of microvascular occlusions [1]. Renal manifestations include hyposthenuria, incomplete renal tubular acidosis, impaired potassium secretion, haematuria and proteinuria [2]. This report describes a woman with sickle cell disease who had IgA nephropathy and a year later developed rapidly progressing renal failure.

Case report

Clinical history

A 19-year-old female, originally from Guinea, had sickle cell disease with numerous vaso-occlusive crises, and she presented with bilateral leg swelling and periorbital puffiness. Creatinine was 140 μmol/L and 24-h proteinuria 14.4 g/day. A renal biopsy showed diffuse mesangial proliferative and crescentic glomerulonephritis (GN) due to IgA nephropathy.

Treatment included 6-month prednisone and IV cyclophosphamide followed by azathioprine. Creatinine fell to 138 μmol/L. A year later, it increased to 485 μmol/L. She had pulmonary oedema, myalgias and pruritus, but no haematuria.

Urinalysis demonstrated 51–100 RBCs per high power field. The spot urine protein:creatinine ratio was 1093.2 mg/mmol. Creatinine was 828 μmol/L, LDL 2.3 mmol/L, white blood cell count 4.7 $\times$ 10^9/L, haemoglobin 104 g/L and platelet count 116 $\times$ 10^9/L. There were schistocytes (3–5/hpf), echinocytes and Howell Jolly bodies. A renal ultrasound showed symmetric normal-sized kidneys with no obstruction. The blood pressure was 180/110 mmHg. Haemodialysis was initiated. A second renal biopsy was performed (Figure 1).

Therewere up to 18 glomeruli, 9 globally sclerosed, 5 segmentally sclerosed, 3 with thrombotic and fibrinoid injury, and 3 cellular crescents. Glomerular capillary walls had focal double contours. Tubular epithelium showed focal cytoplasmic vacuolation, sloughing of cells and prominent hyaline droplet change. Vasa recta showed prominent inflammatory cell accumulation, including marginating neutrophil polymorphs. There was patchy chronic interstitial inflammation and severe tubular atrophy and interstitial fibrosis. Arteries showed moderate fibrous intimal thickening and no vasculitis. Up to three arterioles showed fibrinoid necrosis, some with associated thrombosis, particularly at glomerular vascular poles. Amyloid stain was negative.

Immunofluorescence showed 1+ segmental IgM and C3, consistent with segmental glomerulosclerosis. Therewas non-specific staining of glomerular epithelial cell cytoplasmic granules for IgA, but no mesangial or capillary wall IgA. Glomeruli were negative for IgG, C1q, fibrinogen, kappa and lambda. Arterioles showed 1–2+ staining for IgM, C3, C1q and fibrinogen.

Ultrastructural examination showed platelet and fibrin thombi occluding an arteriole and glomerular capillaries. Glomerular capillary walls were markedly thickened with subendothelial widening, focal subendothelial fibrin deposition, prominent mesangial cell interposition and reduplication of the glomerular basement membrane (GBM). There was widespread epithelial cell foot process effacement with surface microvillous transformation. Mesangial cells surrounded RBC fragments within the mesangial matrix. No immune complex-type deposits were identified.

Featureswere of acute microvascular injury with arteriolar fibrinoid necrosis, arteriolar and glomerular

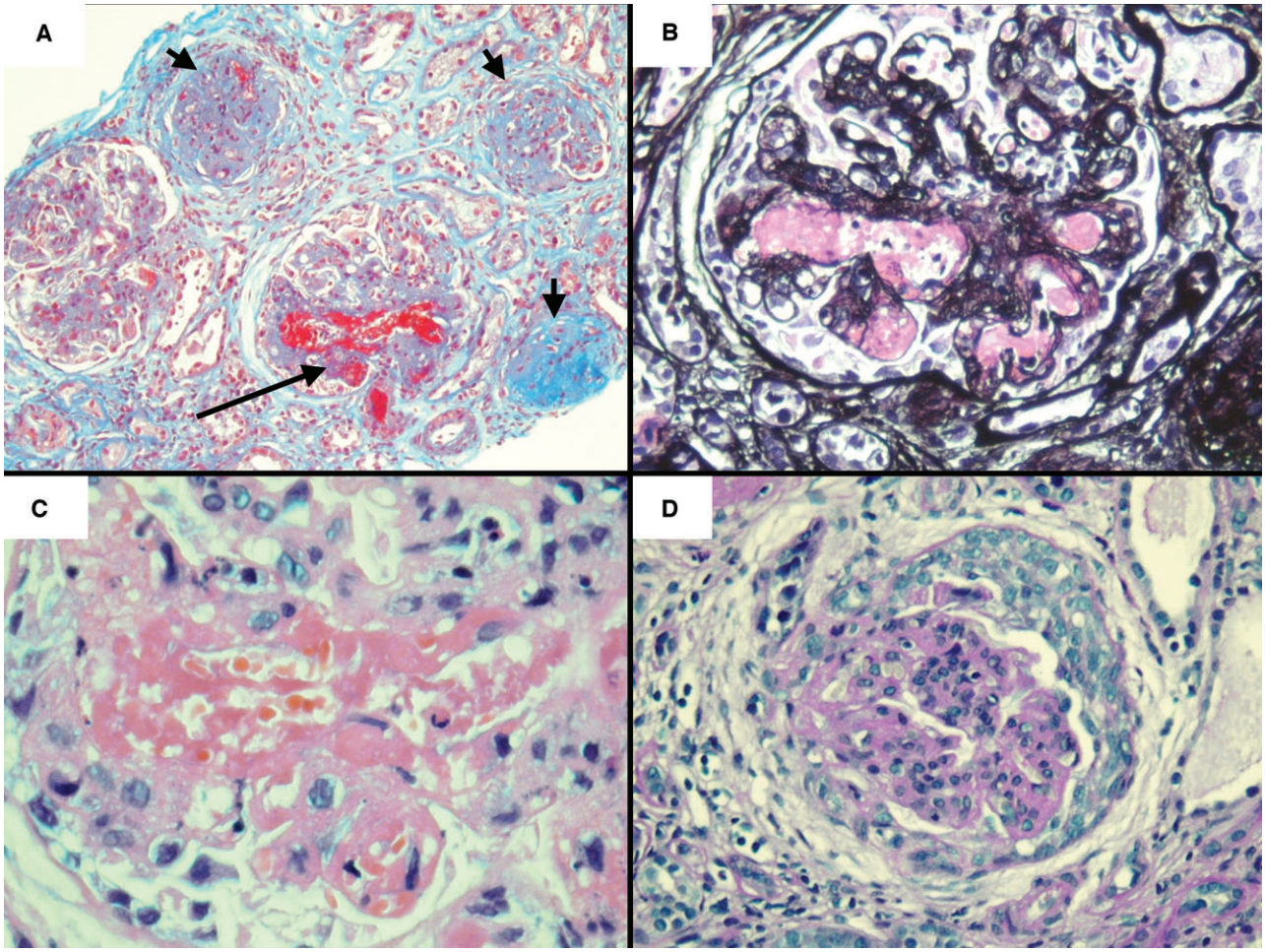

Fig. 1. (**A**) Glomerulus with segmental capillary loop and arteriolar thrombosis (long arrow), globally sclerosed glomeruli (short arrows) and renal interstitial fibrosis, Masson trichrome, ×200. (**B**) Higher power of glomerulus in (**A**) with capillary loop thrombi, PAMS, ×400. (**C**) High power of glomerulus in (**A**) with capillary loop thrombi, fibrinoid injury and mesangiolysis, H & E, ×600. (**D**) Glomerulus with mesangial cell proliferation and circumferential cellular crescent, PAS, ×400.

thrombotic microangiopathy (TMA), andactive glomerular crescentic injury, superimposed upon a chronic membranoproliferative-like pattern of glomerular injury, suggestive of chronic TMA. There were severe chronic irreversible global and focal segmental glomerulosclerosis (FSGS) and patchy moderate-to-severe chronic tubulointerstitial damage. There was no evidence of immune complex-mediated GN in the second biopsy. There was no renal functional recovery. She was transitioned from haemodialysis to peritoneal dialysis.

Discussion

The usual clinical pattern of sickle cell nephropathy is chronic progressive renal failure [2]. Pathologic findings include papillary necrosis, glomerular hypertrophy and perihilar FSGS, immune complex-mediated membranoproliferative GN (MPGN) and an MPGN-like pattern of injury with GBM reduplications but without immune deposits [2,3]. The hypoxic, acidotic and hyperosmolar environment of the inner medulla promotes red cell sickling in the medullary vasa recta, with resultant impairment in blood flow, microthrombi formation, ischaemic microinfarcts and progressive renal medullary injury with papillary necrosis [2].

TMA encompasses non-inflammatory small vessel vasculopathies associated with endothelial or medial myocyte injury and microvascular platelet thrombosis. Commonly recognized causes of renal TMA [4] include haemolytic uraemic syndrome (HUS), thrombotic thrombocytopaenic purpura (TTP), antiphospholipid antibody syndrome, scleroderma, malignant hypertension, disseminated intravascular coagulation, pregnancy-, radiation- and transplant-associated TMA. Our patient did not have enterocolitis or thrombocytopaenia. The antiphospholipid antibody was not measured. She was taking the oral contraceptive pill, a recognized cause of TMA. IgA nephropathy from the first renal biopsy was not corroborated in the second biopsy; renal TMA has been rarely associated with IgA nephropathy [5].

Acute TMA is not a commonly recognized complication of sickle cell disease, with renal vascular congestion by sickled erythrocytes not typically associated with fibrin

thrombi. Pathological features in our case suggest an acute TMA superimposed upon chronic MPGN-like glomerular changes. The MPGN-like glomerular lesion observed in sickle cell disease may be produced by continuous mesangial cell phagocytosis of fragmented red cell masses in glomerular capillaries, with associated remodelling of the GBM and mesangial cell interposition [3]. Similar ultrastructural changes are observed in rats with intravascular fibrin formation [6] and in human renal biopsies with healing HUS [7]. The MPGN-like chronic glomerular lesion of sickle cell disease could be regarded as a chronic TMA-related lesion.

A possible link between sickle cell disease and renal TMA is the presence of circulating microparticles [8], derived from budding cell membranes of endothelium or circulating blood cells. They arise through the cell membrane activation processes and from apoptosis. TTP, characterized by failure to cleave highly pro-thrombotic multimers of von Willebrand factor, is associated with elevated levels of platelet and endothelial-derived microparticles. Microparticles detected in the circulation of patients with sickle cell disease were found to appear during chronic phases and in crises [9]. In the chronic phase, there is haemolysis and the activation of coagulant pathways, resulting in low-grade thrombin generation, depletion of anticoagulants and activation of leucocytes and platelets. These pro-coagulant and pro-inflammatory processes are associated with endothelial cell damage and microparticles derived from endothelial cells, platelets and monocytes. During sickle crises, endothelial damage and coagulation activity increases dramatically, accompanied by a rise in circulating microparticles of platelet, endothelial, RBC and monocyte origin [9,10].

In conclusion, a young female with sickle cell disease, treated for biopsy-proven IgA nephropathy with the resolution of creatinine, a year later presented with acute renal failure. A repeat biopsy showed acute-on-chronic TMA. We suggest that circulating microparticles could be a pathophysiological link between sickle cell disease and the development of renal TMA. This case emphasizes the importance of a further biopsy for acutely declining renal function, even when a definite diagnosis has been made from a previous biopsy.

Conflict of interest statement. None declared.

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