Two cases of self-limiting nephropathies secondary to dengue haemorrhagic fever

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ABSTRACT

We report two cases of dengue haemorrhagic fever which developed self-limiting gross nephrotic-range proteinuria. One patient was a 32-year-old Bangladeshi and the other a 42-year-old Chinese national. Both patients did not have manifestations of renal damage, such as increase in serum creatinine, haematuria or urinary casts. Gross nephrotic-range proteinuria, which was self-limiting due to dengue haemorrhagic fever, has not been previously reported in Singapore. We postulate that this nephrotic-range proteinuria is a manifestation of increased glomerular leakage of protein, due to glomerulonephritis associated with dengue haemorrhagic fever.

Keywords: dengue haemorrhagic fever, immune complexes, nephrotic-range proteinuria, plasma leakage, self-limiting glomerulonephritis

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INTRODUCTION

Dengue is the most prevalent mosquito-borne viral disease in Southeast Asia. It is caused by four dengue virus strains from the genus *Flavivirus* and transmitted by the *Aedes aegypti* mosquito. We report gross nephrotic-range proteinuria in two patients with dengue haemorrhagic fever (DHF) in Singapore.

CASE REPORTS

Case 1

A 32-year-old Bangladeshi man with no past medical illness, presented with fever, chills, myalgia and abdominal pain. He had just arrived from Bangladesh five weeks before presentation, and was working in Singapore. He was admitted to the hospital on the fifth day of illness due to his low platelet count, which was 75,000/uL at presentation, and dropped to 21,000/uL the next day (Table I). He also had chest radiographic evidence of pleural effusion, suggesting plasma leakage. His blood pressure showed a postural drop from 120/80 mmHg lying to 70/50 mmHg on standing, suggestive of intravascular fluid depletion. He was treated with aggressive intravascular fluids and platelet replacement when the platelets dropped below 20,000/uL. He did not have any active bleeding. The dengue virus IgM was positive on admission. A diagnosis of DHF was made.

His liver function test showed transaminitis and low albumin 27 (normal range 37–51) g/L. In view of the low serum albumin levels, the urine protein creatinine ratio was measured, and it was 8.09 (normal range < 0.2, nephrotic range > 3.0) g/day. The patient did not have any haematuria, casts in his urine or evidence of loss of renal function. His serum creatinine level was normal throughout the admission. As nephrotic-level proteinuria is not usually associated with DHF, screening for other causes of proteinuria were done. Post-infectious causes such as hepatitis B, hepatitis C and streptococcus-antistreptolysin O titre (ASOT) were negative. Immunological markers—antinuclear antibodies, anti double-stranded DNA, neutrophil cytoplasmic antibodies and antiglomerular basement membrane antibodies—were negative. His complement level C3 was normal and C4 was raised. By Day 10 of illness, his serum albumin spontaneously normalised to 37 g/L, and a repeat 24-hour urine total protein normalised to 0.06 g/day. We concluded this self-limiting nephrotic-range proteinuria is most likely due to the dengue viral infection.

Case 2

A 42-year-old male Chinese national with no past medical illness, presented with fever, chills, myalgia, headache and petechiae. He has been working in Singapore for the last five years. He was admitted to the hospital on the sixth day of illness with a provisional diagnosis of dengue fever. His platelet count was 100,000/uL at presentation and dropped to 74,000/uL over the next two days (Table II). His dengue virus IgM was positive on the third day of admission. His blood pressure showed a postural drop from 145/90 mmHg lying to 90/60 mmHg on standing, suggestive of intravascular fluid depletion. He was treated with aggressive intravenous fluids.

His liver function test showed transaminitis and low albumin 32 (normal range 37–51) g/L. Due to the

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Table I. Case 1 result trend.

Date	14/3	15/3	16/3*	16/3†	17/3*	17/3†	18/3*	18/3†	19/3	20/3	21/3	27/3
Platelets (× 10^9/L)	75	21	13	16	15	21	37	55	139	150	167	336
Haematocrit (%)	48.6	42.9	44.8	42.0	41.6	41.7	43.7	43.2	44.2	42.6	42.9	41.4
ALT (U/L)		36							52	65		
AST (U/L)		64							74	77		
PT (s)						10.3						
APTT (s)						35.7						
Albumin (g/L)		27							33	37		
UTP/Cr									8.09	0.06		
Creatinine (μmol/L)	116				78		91		89	93		
Urea (mmol/L)	5.7				2.1		1.4		2.9	3.2		
Malaria parasite		Neg										
Dengue IgM Ab		Pos										
Urine culture							Neg					
Creatinine kinase							63					

*morning blood; † afternoon blood; ALT: alanine transferase; AST: aspartate transferase; PT: prothrombin time; APTT: activated partial thromboplastin time; UTP/Cr: Urine protein/creatinine ratio; Pos: positive; Neg: negative

Table II. Case 2 result trend.

Date	02/7	03/7	05/7*	05/7†	06/7	07/7*	07/7†	08/7	09/7	10/7
Platelets (× 10^9/L)	106	100	83	74	83	108	105	144	180	299
Haematocrit (%)	39.9	40.5	43.2	46.0	42.9	40.7	41.5	37.9	38.3	40.0
ALT (U/L)					41	35				
AST (U/L)					49	39				
Albumin (g/L)					36	32				
UTP/Cr								8.97		4.32
Creatinine (μmol/L)				59				61		
Urea (mmol/L)				3.4				2.6		
Dengue IgM Ab						Pos				
Creatinine kinase					65					

*morning blood; † afternoon blood; ALT: alanine transferase; AST: aspartate transferase; UTP/Cr: Urine protein/creatinine ratio; Pos: positive

low serum albumin levels, the urine protein creatinine ratio was measured, and it was 8.97 (normal range < 0.2, nephrotic range > 3.0) g/day. The patient did not have any haematuria, casts in his urine or evidence of loss of renal function, and maintained a normal serum creatinine level throughout the admission. By Day 11 of illness, a repeat urinary protein creatinine ratio was 4.32 g/day, and he was discharged as he was well with no more postural drop, and the platelets were normalised. He was subsequently lost to follow-up.

DISCUSSION

DHF is characterised by rapid-onset capillary leakage, accompanied by thrombocytopenia and altered haemostasis.[1] Both our patients fulfilled the criteria for DHF (fever lasting more than 2–7 days, thrombocytopenia and plasma leakage as evidenced by pleural effusion and hypoproteinaemia) with positive dengue IgM antibody.[1] For Case 1, the patient's haematocrit did not increase. However, this was probably due to the aggressive intravenous fluid resuscitation. Radiologically, he had a pleural effusion. However, in Case 2, the patient's haematocrit went up by about 15% from his baseline, with hypoalbuminaemia.

The gross nephrotic-range proteinuria demonstrated in both our patients is a reflection of dengue-associated glomerulonephritis. *In vivo* studies by Boonpuucknavig and Siripont have shown then the presence of preformed dengue antigen-antibody complexes circulating freely can attach to B-lymphocytes and produce vasculitic lesion, causing haemorrhagic manifestation and glomerular inflammation.[2] In experimental studies, glomerulonephritis was demonstrated in mice with preformed dengue antigen-antibody complex. These mice showed proteinuria and deposits of the immune complexes in the glomeruli of the kidneys. The proteinuria was normalised spontaneously with resolution of the disease.[3]

Plasma leakage, associated with a sudden onset of vascular permeability, is a well-described phenomenon in DHF and dengue shock syndrome. It is thought to be immune-mediated, with increases in interferon and soluble tumour necrosis factors demonstrated in patients with DHF and dengue shock syndrome.[3] The World

Health Organization defines evidence of plasma leakage by haemoconcentration with substantial changes in serial measurements of packed cell volumes, or by the development of pleural effusions or ascitis, or both.[1] Low albumin levels have been described in DHF.[4] Two previous case series of hospitalised dengue patients reported proteinuria (diagnosed on urine analysis), during the acute dengue infection.[5,6] Horvath et al reported 74% of patients hospitalised with dengue in Queensland, Australia, had proteinuria. However, only one elderly patient in the study had clinical features of nephrotic syndrome, and the urinary protein was quantified at 10.8 g/24 hours.[5]

Although our patients had nephrotic level proteinuria, they did not have nephrotic syndrome as peripheral oedema was absent in both patients. The criteria for nephrotic syndrome are low serum albumin (< 30 g/L), urinary protein excretion > 3.5 g/1.73m^2 per 24 hours, peripheral oedema, hypoalbuminaemia (serum albumin < 30 g/L) and hyperlipidaemia. In our patients, the urinary protein loss with associated hypoalbuminaemia was self-limiting and only for a short duration. For oedema to develop, there should be prolonged loss of protein in the urine to exhaust the plasma protein level. Hyperlipidaemia can occur as a response to increased hepatic synthesis of cholesterol and lipoproteins. As the dengue-associated glomerulonephritis is a self-limiting illness, these secondary responses very rarely appear, except for the elderly patient described above.[5]

Nephrotic syndrome has been well documented in other viral infections like hepatitis B and C, and *Hantavirus* spp.[7,8] These are thought to be immune-mediated. Histological descriptions include acute interstitial nephritis, proliferative glomerulonephritis, acute tubular necrosis and mesangial hyperplasia.[9,10] Acute kidney injury with acute tubular necrosis due to shock and multiorgan failure, resulting in rhabdomyolysis, haemolysis with haemoglobinuria, proteinuria, and thrombotic microangiopathy, have been described in patients with dengue infection.[10] Our patients' urinary protein loss, at 8.06 g/dL and 8.97 g/dL, respectively, were in the nephrotic range, and have not been reported in Singapore. Case 1 patient's proteinuria cleared on resolution of the disease. We suspect that Case 2 patient also would have had resolution of the proteinuria; however, we were unable to confirm this as he was subsequently lost to follow-up.

We postulate that the nephrotic-range proteinuria could be a manifestation of an automimmune mechanism that the virus had triggered on the reticuloendothelial system, resulting in glomerular leakage of protein due to glomerulonephritis associated with DHF. Previous studies on immunohistopathological findings of kidney tissue biopsied during the first and third weeks of a dengue illness showed mild proliferation of mesangial cells, depositions of IgG and complement C3, and occasionally IgM in the glomerulus, indicating a mild form of glomerulonephritis.[9] The amount of C3 and immunoglobulins was also less than that seen in the glomerulus of the post-streptococcal group.[9] The possible mechanism of the self-limiting proteinuria could be due to the body's clearance of the immune complexes, resulting in resolution of the plasma leakage and illness.

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