

Case Report

Severe left ventricular systolic dysfunction in a patient with a typical haemolytic–uraemic syndrome treated with rituximab—coincidence or cause?

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Abstract

A 26-year-old female with haemolytic–uraemic syndrome (HUS) refractory to daily plasma exchange was successfully treated with rituximab. Subsequent testing confirmed the presence of mutations in genes encoding complement factor I and CD46. On Day 32 she developed pulmonary oedema, and echocardiography demonstrated severe left ventricular systolic dysfunction. There was no evidence of recent myocardial infarction. Cardiac involvement has been reported, not only in thrombotic thrombocytopenic purpura (TTP) but also with rituximab therapy. However, it is unclear if atypical HUS is also associated with cardiac disease. We recommend echocardiography in all patients with TTP–HUS and in any patients commencing treatment with rituximab.

Keywords: haemolytic–uraemic syndrome; heart failure; renal failure; rituximab

Background

Thrombotic thrombocytopenic purpura and haemolytic–uraemic syndrome (TTP–HUS) are disorders characterized by microangiopathic haemolytic anaemia (MAHA) and classically present with the pentad of MAHA, thrombocytopenia, fever, neurological involvement and renal failure. Our understanding of these diseases has dramatically advanced, and we now know that TTP (which is characterized by predominant neurological involvement) is due in part to decreased activity of a metalloprotease, ADAMTS13. This enzyme cleaves large multimers of von Willebrand factor and its deficiency results in their accumulation. In turn, this results in the development of occluding thrombi in arterioles and capillaries, leading to ischaemic damage to organs. HUS is typically associated with diarrhoea and the presence of a Shiga-like toxin, but cases of ‘atypical HUS’, not associated with diarrhoea, are increasingly recognized. These are now known

to result from genetic abnormalities in the regulation of the complement system. The frequency and clinical sequelae of cardiac abnormalities in TTP–HUS are unknown, but myocarditis and myocardial infarction have been reported in case reports and small retrospective studies. Autopsy findings have demonstrated widespread arteriolar occlusions, myocardial necrosis and thrombosis [1–4].

Case report

A 26-year-old female with no past medical history presented with a 5-day history of a diarrhoeal illness on return from holiday abroad. On examination, she was febrile, pale and jaundiced, with involuntary clonic twitching of her right arm and leg. Full blood count revealed anaemia (Hb 8.4 g/dL) and thrombocytopenia (platelets 28×10^9 /dL), and a blood film examination showed red cell fragments. Serum bilirubin was 44 μ mol/L, lactate dehydrogenase 3702 U/L, urea 24 mmol/L and creatinine 335 μ mol/L. Culture for *Escherichia coli* 0157 was negative. A presumptive diagnosis of TTP was made and the patient was treated with daily plasma exchange, fresh frozen plasma, packed red cells and methylprednisolone. There was no response to treatment after 8 days with evidence of ongoing haemolysis. Second-line therapy with rituximab in a dosing regime of intravenous infusions of 600 mg on Days 8, 15 and 22 was introduced. This is a monoclonal antibody against the CD-20 antigen present on B-lymphocytes and has been used successfully to treat refractory TTP. Despite this, her renal function progressively declined, creatinine reaching 600 μ mol/L, and she required haemodialysis on Day 11. Daily ultrafiltration continued for 9 days and thereafter her renal function recovered slowly, with no evidence of fluid overload. On Day 32, she became acutely unwell with evidence of pulmonary oedema. Serum albumin was 34 g/dL and creatinine 434 μ mol/L. She responded to intravenous furosemide and ultrafiltration of 1.5 L with no further renal support following this treatment. Electro-

cardiograms (ECGs) showed a sinus tachycardia with T-wave inversion in leads I, III, aVL and V4–V6 but no evidence of ST-segment deviation or arrhythmia. There were no sequential ECG changes, and serum troponin I was only mildly elevated at 0.28 µg/L. Creatinine kinase was not checked but there was no rise in serum aspartate aminotransferase. Urgent transthoracic echocardiography showed global severe hypokinesis of the left ventricle, with a left ventricular end-diastolic diameter of 6 cm. Estimated left ventricular ejection fraction was 20%. The right ventricle contracted well and no pericardial effusion or valvular abnormality was documented. Her clinical cardiac status stabilized with diuretic therapy and the introduction of beta blockade and an angiotensin-converting enzyme inhibitor. Her renal function improved with creatinine stabilizing at 240 µmol/L. Despite her improved clinical status, a pre-discharge echocardiogram on Day 40 revealed no improvement in left ventricular function. Subsequent genetic testing revealed mutations in complement factor I and CD46, confirming a diagnosis of atypical HUS.

Discussion

Pathological studies of TTP–HUS patients demonstrate cardiac involvement [1–4], but the true incidence of myocardial involvement in TTP–HUS is unknown. Several case reports have described myocardial infarction (MI), and a recent case series of 85 patients identified 13 (15%) myocardial infarctions [5]. This series suggested that a diagnosis of TTP, rather than HUS, was a strong risk factor for cardiac involvement. Cardiogenic shock was reported in a 49-year-old man with TTP and an autopsy showed a diffuse myocardial necrosis due to microvascular thrombosis [6]. Left ventricular systolic dysfunction has been reported during the acute phase of HUS and subsequently with or without recovery of left ventricular function [7–9]. The incidence of ventricular dysfunction in cases of TTP–HUS is, however, unclear and to our knowledge this is the first case report of such involvement in a patient with proven mutations in genes encoding complement regulatory factors.

Rituximab carries a boxed warning for severe infusion reactions including pulmonary infiltrates, acute respiratory distress, MI or cardiogenic shock. Recently, cardiogenic shock was reported in a 20-year-old female treated ‘successfully’ with rituximab for refractory TTP, but in that case her ventricular function had recovered prior to hospital discharge [10]. The aetiology of cardiotoxicity following rituximab remains uncertain. The mechanisms for

ventricular dysfunction in our case are speculative and include a viral myocarditis, ischaemic insult secondary to microangiopathy or ventricular dysfunction secondary to rituximab therapy. The lack of either chest pain or cardiac biomarker elevation and ST-segment deviation on the ECG would exclude acute myocardial infarction. However, the absence of left ventricular functional assessment prior to rituximab therapy renders the latter aetiologies as merely speculative. We did not elect to biopsy her myocardium, and cardiac magnetic resonance imaging was contraindicated in view of her persisting renal impairment.

Conclusion

We would recommend echocardiographic assessment of ventricular function in patients with TTP–HUS and in any patients commencing treatment with rituximab.

Conflict of interest statement. None declared.

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