Primary glomerulonephritis with isolated C3 deposits [8] is a rare entity, of which the general clinical picture is consistent with our patient presentation, i.e. episodes of gross haematuria and/or persistent or recurrent micro-haematuria and/or proteinuria and/or hypertension.

Initial presentation of the glomerular disease was somehow misleading because of atypical features suggesting systemic lupus erythematosus which was invalidated on renal biopsy. On the other hand, several lines of evidence strongly suggested that MPGN was a paraneoplastic syndrome of HCL in our patient: ANA were negative; the two diseases are very rare; they were discovered concomitantly and responded both completely and simultaneously to HCL therapy. Although cladribine seems to have some activity in autoimmune disorders including systemic lupus erythematosus [9], there is, to our knowledge, no published data on cladribine in other glomerular diseases.

Glomerulonephritis may predate the diagnosis of a lymphoproliferative disease, and patients with suspicious glomerular disease should be screened and monitored for possible lymphoproliferative diseases.

Conflict of interest statement. None declared.

Myocardial infarction is a complication of factor H-associated atypical HUS

Marion Sallée1, Laurent Daniel2, Marie-Dominique Piercechi3, Dominique Jaubert1, Veronique Fremeaux-Bacchi4, Yvon Berland1 and Stephane Burtey1

1Centre de néphrologie et transplantation rénale, AP-HM, Hôpital de la Conception, Université de la Méditerranée, Marseille, France, 2Service d’anato-mo-pathologie, AP-HM, Hôpital de la Timone, Marseille, France, 3Service de médecine légale et droit de la médecine, AP-HM, Hôpital de la Timone, Marseille, France and 4Service d’immunologie, AP-HP, Hôpital Georges Pompidou, Paris, France

Correspondence and offprint requests to: Stéphane Burtey; E-mail: stephaneb@ap-hm.fr

Abstract

Cardiac complications are frequently seen in thrombotic thrombocytopenic purpura related to ADAMTS13 deficiency. We describe the case of a 43-year-old woman who was diagnosed with an atypical haemolytic–uraemic syndrome (aHUS) associated with a pathogenic mutation in the factor H gene (C623S). After 15 days of treatment, she suffered a sudden cardiac arrest and died despite intensive resuscitation attempts. She showed only one cardiovascular risk factor, hypercholesterolaemia. Her sudden death was secondary to cardiac infarction related to a coronary thrombotic microangiopathy. This is the first case of aHUS related to a mutation in the factor H gene associated with cardiac microangiopathy. This case emphasizes the need to screen for cardiac complication during the treatment of aHUS.

Keywords: atypical haemolytic–uraemic syndrome; coronary thrombotic microangiopathy; factor H mutation; sudden death

Background

Thrombotic microangiopathy (TMA) is characterized by haemolytic anaemia, thrombocytopenia and microvascu-
Myocardial infarction is a complication of factor H-associated atypical HUS.

The association of a malar rash, haemolytic anaemia and nephrotic syndrome with acute renal failure suggested systemic lupus erythematosus. Corticosteroid treatment was commenced with three pulses of 500 mg/kg followed by 1 mg/kg/j before a kidney biopsy was performed. Dialysis sessions were initiated. The patient was transfused with two RBC packs. No more transfusions were done. The corticosteroids initially corrected the platelet count. All immunological tests (antinuclear antibodies, anti-DNA antibodies, ANCA, cryoglobulinemia, rheumatoid factor) were negative. Direct and indirect Coombs tests were negative. C3 antigen (Ag) was 638 mg/L (normal range, 660–1250 mg/L), C4 Ag was 298 mg/L (normal range, 93–380 mg/L), factor B Ag was 85 mg/L (normal range, 90–320 mg/L) and factor H Ag was 64% (normal range, 65–140%). Activity of ADAMTS13 was 60% with no antibodies against ADAMTS13.

A kidney biopsy was performed when platelet counts allowed it. The kidney biopsy revealed typical TMA (Figure 1).

Plasma exchanges were performed daily, 14 days after the onset of her symptoms, with 3 L of solvent detergent plasma (50 ml of plasma per kilogramme of body weight). The plasma exchanges were done with a femoral venous catheter of 14 Fr. We used an HF440 generator (Infomed SA) for plasma exchanges. Thirteen days after the beginning of daily plasma exchanges, haematological parameters improved with an increase in haptoglobin, normalization of LDH, correction of thrombocytopenia and a decrease in schistocytes (1% of RBC count).

On day 15, after the beginning of plasma exchange, the patient suffered a sudden malaise with neck pain. Circulatory arrest associated was identified with pulse rate under 25/min. Heart massage was immediately initiated followed by mechanical ventilation. Rapidly, EKG showed non-electrical cardiac activity. Because heart activity did not resume after 10 boluses of 1 mg adrenalin, a cardiac ultrasound scan was performed. A pericardial effusion with tamponade was observed. Pericardial paracentesis allowed the evacuation of 300 cc of blood. However, the patient died, despite intra-thoracic cardiac massage. Troponin I-C taken at the beginning of resuscitation was 2.212 ng/ml (normal range, 0–0.04 ng/ml). A necropsy was performed. The delay between death and tissues sampling was <12 h. Necropsy revealed a myocardial infarction with no obstruction of the coronary arteries. In the heart, multiple microscopic areas of infarction (cardiomyocytes necrosis) were present.
in the myocardium of both ventricles dating 15 days to 24 h (Figure 2). No coronary thrombi were highlighted. There was no atherosclerotic lesion on coronary arteries. Pathology examination showed vessel wall thickening and subendothelial oedema with no vessel thrombi. The small vessels had endothelial swelling suggestive of TMA. Immunohistochemistry revealed an activation of the final pathway of complement in the small coronary vessels and in infarcted cardiomyocytes. C5b9 expression is an early marker of myocardial infarction, not specific of aHUS. It was specific of infarction. This staining is absent during autolytic changes [9]. The C5b9 positivity confirmed the myocardial infarction as the aetiology of death. Diffuse microscopic myocardial infarctions with normal coronary arteries are certainly secondary to aHUS.

Alternative complement pathway was studied and genetic mutations were explored. The patient showed alternative pathway activation with decreased plasma levels of C3 and factor B. The plasma concentration of FH protein was low (64% of normal value), suggesting a heterozygous FH deficiency. A nucleotide substitution leading to the change of a cysteine to another amino acid was found in SCR 10 at Position 623 in the factor H gene (TGT > TCT; Cys623Ser). This genetic abnormality was absent in a sample of more than 100 individuals (>200 chromosomes investigated) and was not previously reported in patients with aHUS.

Thirty years ago, her second cousin had suffered from aHUS with renal failure leading to dialysis. Renal transplantation was performed 2 years after the beginning of dialysis. She lost her graft 10 days after transplantation because of TMA recurrence. We identified the same mutation (C623S), which allowed us to make the diagnosis of aHUS related to CFH mutation, 30 years after the beginning of the disease.

Discussion

Sudden death can be seen in the course of TMA. Clinical and biological examinations can serve to exclude ionic abnormalities and non-cardiac causes. In our case, the final diagnosis was sudden death secondary to cardiac infarction related to a coronary TMA associated with a pathogenic mutation in factor H. We could not definitely affirm that infarction was related to aHUS because no microcirculatory thrombosis was detected within the myocardium contrary to the renal tissue, but intra-myocardial TMA was highly suggested by multifocal myocyte necrosis and endothelial swelling.

Besides neurological complications, cardiac injury in TTP is recognized as one of the leading causes of death [10]. A low level of ADAMTS13 with an accumulation of ultra large multimers of von Willebrand factor is associated with adverse outcome in myocardial infarction [11]. Furthermore, free haemoglobin due to haemolytic anaemia can capture nitric oxide (NO), which results in decreased NO. This decrease could be associated with vasoconstriction and platelet activation [12]. Although pathology findings often reveal microthrombi and infarction, clinical cardiac abnormalities are rarely seen [13].

Cardiac complications in HUS are not as well described as those in TTP. Yet, 10 to 25% of patients with aHUS die as a result of the syndrome. The heart could be an unrec-
Myocardial infarction is a complication of factor H-associated atypical HUS

Table 1. Case report of cardiac involvements in HUS course

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient</th>
<th>Cause of HUS</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Time after onset (days)</th>
<th>Cardiac disease</th>
<th>Troponin level</th>
<th>Cardiac outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eckart et al. [13]</td>
<td>1</td>
<td>PI</td>
<td>M</td>
<td>1.87</td>
<td>10</td>
<td>MI</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>VTEC</td>
<td>F</td>
<td>2</td>
<td>4</td>
<td>DCM</td>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>VTEC</td>
<td>F</td>
<td>2.1</td>
<td>90</td>
<td>DCM</td>
<td>28</td>
<td>Recovery</td>
</tr>
<tr>
<td>Thayu et al. [14]</td>
<td>4</td>
<td>VTEC</td>
<td>M</td>
<td>9</td>
<td>6</td>
<td>MI</td>
<td>16</td>
<td>Recovery</td>
</tr>
<tr>
<td>Nayak et al. [15]</td>
<td>5</td>
<td>Toxic</td>
<td>M</td>
<td>55</td>
<td>1</td>
<td>MI</td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>Abu-Arafeh et al. [16]</td>
<td>6</td>
<td>VTEC</td>
<td>F</td>
<td>13</td>
<td>2</td>
<td>Myocarditis</td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td>Thomas et al. [17]</td>
<td>7</td>
<td>PI</td>
<td>F</td>
<td>2</td>
<td>4</td>
<td>MI</td>
<td></td>
<td>Death</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>VTEC</td>
<td>M</td>
<td>4</td>
<td>5</td>
<td>DCM</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>Askiti et al. [18]</td>
<td>9</td>
<td>VTEC</td>
<td>F</td>
<td>1.8</td>
<td>6</td>
<td>Myocarditis</td>
<td>43</td>
<td>Recovery</td>
</tr>
<tr>
<td>Tobias [19]</td>
<td>10</td>
<td>PI</td>
<td>M</td>
<td>0.75</td>
<td>7</td>
<td>DCM</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>Mohammed et al. [20]</td>
<td>11</td>
<td>VTEC</td>
<td>M</td>
<td>2</td>
<td>5</td>
<td>Tamponade</td>
<td>7.8</td>
<td>Recovery</td>
</tr>
<tr>
<td>Walker et al. [21]</td>
<td>12</td>
<td>VTEC</td>
<td>F</td>
<td>2</td>
<td>120</td>
<td>DCM</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>Poultan et al. [22]</td>
<td>13</td>
<td>VTEC</td>
<td>F</td>
<td>1.8</td>
<td>56</td>
<td>DCM</td>
<td></td>
<td>Improvement</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>Unknown</td>
<td>M</td>
<td>8</td>
<td>25</td>
<td>DCM</td>
<td></td>
<td>Recovery</td>
</tr>
<tr>
<td>Birk et al. [23]</td>
<td>15</td>
<td>VTEC</td>
<td>F</td>
<td>6</td>
<td>5</td>
<td>Tamponade</td>
<td>4</td>
<td>Death</td>
</tr>
<tr>
<td>Leray et al. [24]</td>
<td>16</td>
<td>Post-partum</td>
<td>M</td>
<td>24</td>
<td>90</td>
<td>DCM</td>
<td></td>
<td>Improvement</td>
</tr>
</tbody>
</table>

Pl, post infectious; MI, myocardial infarction; DCM, dilated cardiomyopathy.

Cardiac injuries due to consequences of microangiopathy in cardiac tissue were described in three cases. The course of cardiac injury in our patient and in those cases was similar. Clinical presentation was severe and death occurred rapidly. Troponin level was high, and pathology results confirmed microangiopathy of small heart vessels. Myocardial tissue could be affected by the same anomalies of microvascular circulation as is those observed in the kidney during HUS. This is the first time that cardiac injury was described in aHUS associated with mutation in CFH (TGT > TCT; Cyst623Ser). It could be of great interest to systematically evaluate cardiac activity in a well-genotyped cohort of aHUS to identify whether cardiac injury is more frequently associated with particular mutated genes.

In the literature, it is unclear how cardiac injury of TMA could be detected and how it could be treated. Because of the atypical presentation and the severity of the prognosis of cardiac infarctions, we recommend monitoring cardiac enzymes like troponin I, as well as 12-lead EKG, daily. The monitoring should be very frequent particularly when platelet count is normalized. If troponin assay and/or EKG suggest cardiac injury, a cardiac sonogram is necessary to identify segmental or diffuse myocardial dysfunction. If patients have classical risk factors of atherosclerosis, a coronaryography should be done rapidly to eliminate a stenosis on heart arteries. Management should include antiplatelet therapy, heparin and beta blockers, as that used for acute coronary syndrome of more typical aetiology.

In conclusion, this is the first report, to our knowledge, of a case of cardiac injury in aHUS due to genetic mutation in factor H gene with a poor outcome. Patients with aHUS and Stx-associated HUS, like patients with TTP, have to be monitored for cardiac injury. We believe that troponin and EKG monitoring is a good course of action and should be systematically performed. It should be of interest to study cardiac injury in genotyped aHUS to identify mutations.

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Conflict of interest statement. None declared.

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EBV-positive B cell cerebral lymphoma 12 years after sex-mismatched kidney transplantation: post-transplant lymphoproliferative disorder or donor-derived lymphoma?

Paul J. Phelan1, Rory K.J. Murphy2, Michael Farrell3, Orna O'Toole3, Josie Heffeman3, Donncha O'Brien2, Oscar Breathnach2 and Peter J. Conlon1

1Department of Nephrology, Beaumont Hospital, Dublin, Ireland, 2Department of Neurosurgery, Beaumont Hospital, Dublin, Ireland, 3Department of Neuropathology, Beaumont Hospital, Dublin, Ireland and 4Department of Oncology, Beaumont Hospital, Dublin, Ireland

Correspondence and offprint requests to: Paul J. Phelan; E-mail: paulphel@gmail.com

Abstract

We present a follow-up case report of possible transmission of lymphoma 12 years after deceased-donor renal transplantation from a male donor who was found at autopsy to have had an occult lymphoma. The female recipient underwent prompt transplant nephrectomy. However, 12 years later, she presented with cerebral B cell lymphoma. A donor origin for the cerebral lymphoma was supported by in situ hybridization demonstration of a Y chromosome in the lymphoma. There was a dramatic resolution of the cerebral lesions with taping of immunosuppression and introduction of rituximab treatment. The

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