CASE REPORT

Nodular regenerative hyperplasia of the liver and coeliac disease: potential role of IgA anticardiolipin antibody

A Austin, E Campbell, P Lane, E Elias

Nodular regenerative hyperplasia (NRH) of the liver is a rare disorder that is often associated with non-cirrhotic portal hypertension. We describe two cases of NRH in individuals with adult coeliac disease and IgA anticardiolipin antibodies. We discuss the potential impact of this observation on the understanding of the pathogenesis of NRH.

NRH is characterised by the presence of nodules of regenerative hepatocytes, without fibrous septa, distributed diffusely across the hepatic parenchyma. Although its pathogenesis remains unclear, NRH is thought to result from liver regeneration after ischaemia induced injury. An intrahepatic microvascular occlusive mechanism has been proposed and a prothrombotic disorder has been reported in half of cases presenting with non-cirrhotic portal hypertension.

Antiphospholipid antibodies (aPL) are a heterogeneous group of circulating autoantibodies found in the sera of healthy subjects and patients with autoimmune and infectious diseases. They have been implicated in the occurrence of thrombocytopenia and thrombotic events. An association between IgG aPL and NRH was first reported in patients with systemic lupus erythematosus. We discuss two cases of NRH complicated by portal hypertension and associated with IgA anticardiolipin antibodies (aCL) in patients with adult coeliac disease. We discuss the possible relationships between coeliac disease, IgA anticardiolipin antibodies, and NRH.

CASE REPORTS

Case 1

A 55 year old female presented with ascites, weight loss, and thrombocytopenia (76 × 10^9/l). She had been diagnosed with coeliac disease 24 years earlier. Compliance with a gluten free diet had been suboptimal. Her liver function tests were abnormal (AST 114 (normal range 5–43), ALT 330 (normal range 17–330), bilirubin 39 μmol/l (normal range 34–51), albumin 32 g/l (normal range 30–45)). She was positive for IgA anticardiolipin antibodies. Immune screen, including assays for protein C and S (function and protein), antithrombin III, and activated protein C resistance was negative in both cases. Results of aCL antibody and anti-β1 glycoprotein 1 antibody assays are shown in table 1.

DISCUSSION

We have reported two cases of NRH associated with IgA aCL and longstanding coeliac disease (poor dietary compliance). Our current understanding of NRH is that obliteration of small portal branches causes atrophy of downstream lobules and initiates compensatory hyperplasia in adjacent lobules with an intact portal venular supply. A number of thrombophilic disorders, including polycythemia vera, primary thrombocytopenia, protein S deficiency, and IgG antiphospholipid syndrome (APS) are associated with NRH. APS is a systemic autoimmune disorder characterised by a combination of arterial and/or venous thrombosis or recurrent pregnancy loss, and thrombocytopenia with the presence of elevated titres of aPL antibodies. aPL are autoantibodies directed against anionic phospholipids or protein/ phospholipid complexes (commonly containing β2 glycoprotein I (β2-GPI) or prothrombin, but also protein C, protein S, and annexin V) measured in solid phase immunoassays as aCL.

In addition, features of a chronic biliary process were present but not suggestive of primary biliary cirrhosis. There was no evidence of cirrhosis. A biopsy taken five years earlier at the referring hospital showed an identical process. Following liver biopsy, she developed intractable haemorrhage with features of disseminated intravascular coagulation and died.

Case 2

A 35 year old male presented with ascites, weight loss, and thrombocytopenia (42 × 10^9/l). A liver biopsy demonstrated NRH and he was diagnosed with coeliac disease on duodenal biopsy the following year. He took a gluten free diet intermittently and suffered episodic ascites and confusion. Age 43 years, he was referred for liver transplantation but prior to assessment suffered a stroke (right parietal lobe infarct). His liver function tests were abnormal (AST 1032 (normal range 5–43), ALT 53 (normal range 17–330), bilirubin 39 μmol/l (normal range 1–22), albumin 32 g/l (normal range 34–51), INR 1.3). He remained positive for IgA endomyosal antibodies and duodenal biopsy demonstrated persistent subtotal villous atrophy. The liver was small but he improved slowly on a strict gluten free diet. Acute portal vein thrombosis precipitated a further deterioration and he died.

In both cases, total IgA levels were elevated but autoantibodies, including antimitochondrial and antineutrophil cytoplasmic antibodies, were negative. A full thrombophilia screen, including assays for protein C and S (function and protein), antithrombin III, and activated protein C resistance was negative in both cases. Results of aCL antibody and anti-β1 glycoprotein 1 antibody assays are shown in table 1.

Abbreviations: NRH, nodular regenerative hyperplasia; aCL, anticardiolipin antibodies; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; AST, aspartate aminotransferase; ALP, alkaline phosphatase; INR, international normalised ratio; β2-GPI, β2 glycoprotein 1
antibodies or detected in phospholipid dependent clotting tests as lupus anticoagulant.

In the cases described here, aCL antibodies were associated with abnormal thrombosis, bleeding, and prolonged persistent thrombocytopenia in the absence of other features of hypersplenism. The exact mechanism by which aCL antibodies are produced is unclear. Anionic phospholipids (for example, phosphatidylserine) are regular constituents of the inner leaflet of the cell membrane that are only exposed on the outside of the cell membrane during apoptosis, or by damaged endothelial cells and activated platelets during blood coagulation. In the latter situation, membranes containing phosphatidylserine provide the catalytic surface that serves as a point of assembly for the prothrombinase complex. In an animal model, systemic exposure to apoptotic cells induced the formation of aCL. We postulate that apoptosis is the link between coeliac disease and an aPL associated vasculopathy which leads to NRH. Coeliac disease is caused by an abnormal T cell mediated inflammatory response to dietary gluten and the hallmark autoantibody is produced against the tissue and cell associated protein transglutaminase. The mechanism thought to evoke this anti-self antibody begins with transglutaminase cross linking and forming a complex with gliadin which is rich in glutamine. Transglutaminase specific B cells take up gluten/transglutaminase complexes and present T cell epitopes to gluten specific T cells, resulting in T cell help for the production of antibodies against the self-protein transglutaminase. Transglutaminase is also expressed in apoptotic cells where it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents. We hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents, we hypothesise that when it cross links glutamine residues in membrane proteins, thereby protecting apoptotic cells from disintegrating and releasing their contents.

Table 1 Results of anticardiolipin antibody and anti-β2 glycoprotein 1 antibody assays in the two patients

<table>
<thead>
<tr>
<th>Anticardiolipin antibody (IU/ml)</th>
<th>Anti-β2 glycoprotein 1</th>
</tr>
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<tbody>
<tr>
<td><strong>Case 1</strong></td>
<td></td>
</tr>
<tr>
<td>IgG (NR 0–12)</td>
<td>12</td>
</tr>
<tr>
<td>IgM (NR 0–10)</td>
<td>10</td>
</tr>
<tr>
<td>IgA (NR 0–13)</td>
<td>44</td>
</tr>
<tr>
<td><strong>Case 2</strong></td>
<td></td>
</tr>
<tr>
<td>IgG (NR 0–12)</td>
<td>12</td>
</tr>
<tr>
<td>IgM (NR 0–10)</td>
<td>10</td>
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</tbody>
</table>

NR, normal range.

lymphoid tissue. The concentration of IgA aCL would be expected to be higher in portal venous blood compared with the systemic circulation, and portal vein radicles would be the most likely site to be affected by thrombotic complications.

In conclusion, we have described two cases of NRH associated with IgA aCL and evidence of poorly compliant coeliac disease. We suggest T cell help from gluten specific T cells is responsible for driving the IgA autoantibody response to both transglutaminase and protein/phospholipid complexes, leading to the formation of IgA aCL. IgA aCL then trigger thrombosis in small portal vein radicles, which drain the inflamed small intestine, leading to liver injury with consequent hyperplasia of the surrounding tissue. This observation adds to the list of prothrombotic conditions such as primary myeloproliferative disorders, anticoagulant protein deficiencies, and APS associated with anti-citrullinated portal hypertension.

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