Membranous glomerulonephritis secondary to *Borrelia burgdorferi* infection presenting as nephrotic syndrome

Sir,

A few months following a tick bite an adult patient presented with progressive oedema, hypoalbuminaemia and nephrotic range proteinuria. Serology was positive for *Borrelia burgdorferi* and renal biopsy confirmed secondary membranous glomerulonephritis (MGN).

A 64-year-old male sustained a tick bite on his left leg whilst holidaying on an island near Stockholm. There was no localized reaction or febrile illness associated with the bite. Over the next few months he experienced progressive oedema. Blood tests showed elevated serum creatinine at 147 μmol (106 μmol 2 months prior to holiday), serum albumin 11 g/L and serum cholesterol/HDL ratio 28.8. Urine dipstick showed 4+ of protein and 1+ of blood. Twenty-four-hour urinary collection for protein excretion was 15.46 g/24 h (<0.15 g/24 h). Hepatitis serology and autoimmune screen were negative and complement levels were normal.

Initial enzyme immunoassay to *Borrelia* C6 peptide was reactive. This was followed by western immunoblot which was *Borrelia burgdorferi* IgG antibody positive and IgM antibody negative, consistent with recent infection. The patient was treated with doxycycline 100 mg twice daily for 1 month.

Ultrasound of the renal tract revealed normal sized kidneys and a renal biopsy was performed. Histological examination showed diffuse thickening of the glomerular basement membrane (GBM). Immunohistology demonstrated IgG and C3 in a diffuse granular intensive reaction along the GBM in a membranous pattern. Electron microscopy revealed large electron dense deposits on the mesangial surface.

The patient is on an angiotensin-converting enzyme inhibitor to reduce the intraglomerular pressure, thereby reducing the rate of his disease progression, and on warfarin therapy to reduce the risk of thrombotic complications. His oedema has subsided and the proteinuria has decreased to 650 mg/mmol/L on a recent urine PCR (protein/creatinine ratio) determined in our clinic.

**Table 1.** Patient and clinical characteristics between the two groups. PTH (intact parathyroid hormone), hsCRP (high-sensitivity C-reactive protein), 25(OH)D3 (25-hydroxyvitamin D3)

<table>
<thead>
<tr>
<th></th>
<th>CKD-rP n = 10 (SD)</th>
<th>No CKD-rP n = 11 (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kt/V</strong></td>
<td>1.5 (0.40)</td>
<td>1.3 (0.28)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>66.2 (12.7)</td>
<td>66.5 (13.9)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Male [n (%)]</strong></td>
<td>5 (50.0)</td>
<td>8 (72.7)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Female [n (%)]</strong></td>
<td>5 (50.0)</td>
<td>3 (27.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Time on haemodialysis in months</strong></td>
<td>40.6 (30.5)</td>
<td>38.7 (50.1)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Current use of 1-OH-vitamin D</strong></td>
<td>0.5 (0.5)</td>
<td>0.7 (0.5)</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Current use ofcinacalcet</strong></td>
<td>0.3 (0.5)</td>
<td>0.5 (0.5)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>PTH (ng/L)</strong></td>
<td>317.5 (334.0)</td>
<td>525.8 (474.3)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Fetuin A (g/L)</strong></td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Corrected calcium</strong></td>
<td>2.3 (0.2)</td>
<td>2.2 (0.2)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Calcium (mmol/L)</strong></td>
<td>2.2 (0.2)</td>
<td>2.2 (0.2)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Protein (g/L)</strong></td>
<td>69.3 (4.7)</td>
<td>68.4 (4.5)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Albumin (g/L)</strong></td>
<td>35.7 (3.3)</td>
<td>35.7 (5.9)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>HsCRP (mg/L)</strong></td>
<td>12.5 (9.8)</td>
<td>4.1 (3.0)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>25(OH)D3 (µg/L)</strong></td>
<td>13.9 (4.0)</td>
<td>14.2 (6.3)</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Phosphate (mmol/L)</strong></td>
<td>1.8 (0.6)</td>
<td>1.8 (0.4)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

doi: 10.1093/ndtplus/sfp161

Conflict of interest statement. None declared.


Most membranous glomerulonephritis is idiopathic but MGN may be secondary to immunological conditions, infections (hepatitis B and C, malaria), neoplasms or drugs.

1 Department of Nephrology, Thomas Mettang
Deutsche Klinik für Diagnostik, Wiesbaden, Germany, Uwe Matterné
2 Clinical Social Medicine, University Hospital Heidelberg, Heinz Jürgen Roth
3 Endocrinology/Oncology, Limbach Laboratory, Heidelberg, Elke Weisshaar
4 Clinical Social Medicine, Occupational and Environmental Medicine, University Hospital Heidelberg, Germany

E-mail: T_Mettang@t-online.de


doi: 10.1093/ndtplus/sfp161
Bone morphogenic protein-7: a new prognostic marker for acute kidney injury?

Sir,
Bone morphogenic protein-7 (BMP-7), also known as osteogenic protein-1 (OP-1), is one of the members of the transforming growth factor β (TGF-β) superfamily [1]. This protein was originally identified as a regulator of cartilage and bone formation. However, BMPs have also been shown to regulate the growth, differentiation and migration of various cell types, including epithelial, mesenchymal, neuronal and hematopoietic cells [2].

Acute kidney injury (AKI)—characterized by a sudden loss of the ability of the kidneys to excrete nitrogenous waste, and to maintain electrolyte and fluid balance—is a frequently encountered clinical problem, especially in the intensive care unit patients. Despite some advances in the management of this condition, unfortunately the morbidity and mortality rates of established AKI still remain high (30–70%) [3]. Acute renal failure occurs as a result of a sudden decrease in renal blood flow, toxic or obstructive insult to the renal tubule or inflammation in the tubulointerstitial. The subsequent dysfunction and loss of tubular epithelial cells is of key importance for the pathophysiological consequences of the syndrome. Contrast-induced nephropathy (CIN) is a distinct type of AKI. Although the pathophysiological processes of CIN are not completely understood, many potential mechanisms for renal injury have been proposed—including contrast-media-induced vasoconstriction resulting in reduction in renal blood flow, direct tubular toxicity and free radical and oxidative injury to tubular cells [4].

Tubular epithelial cells (TECs) are a major source of chemokines, cytokines (such as interleukin-6) and growth factors (such as tumour necrosis factor-α) and they play an important role in the initiation of interstitial inflammation. Furthermore, TECs contribute to the progression of renal fibrosis by undergoing an epithelial–mesenchymal transition (EMT), and leading to accumulation of activated fibroblasts in the interstitium [5].

Several studies showed that the principal target of BMP-7 in the kidney was TECs [6]. It is also demonstrated that BMP-7 decreases the secretion of pro-inflammatory cytokines and growth factors by TECs and reverses epithelial-to-mesenchymal transition, while it acts as an antagonist of TGF-β1-induced E-cadherin downregulation [7,8].

Acute kidney injury associated with tubular necrosis leads to reduction in the expression of tubular BMP-7, and after recovery of tubular and glomerular damage, BMP-7 expression is restored [9]. It is demonstrated that BMP-7 can inhibit EMT involving tubular epithelial cells, resulting in potential repair of injured tubules [8]. Furthermore, administration of exogenous rhBMP-7 accelerates the repair of the injured kidney in animal models [10]. Those findings suggest that BMP-7 plays a critical role in the maintenance of kidney homeostasis [9].

In summary, these data suggest that BMP-7 is an important regulator of the tubular epithelial cell function, inflammatory response and epithelial–mesenchymal transition. Reduced expression of BMP-7 may contribute to the fibrotic response, and its administration may ameliorate renal injury. We speculate that by potential mechanisms of repairing injured tubules, BMP-7 has a critical role in recovery of AKI and it may have a prognostic value. Measuring BMP-7 levels might predict the development of CIN and administering rhBMP-7 to high-risk groups (such as predisposed subjects to CIN, requiring contrast investigations) might prevent the development of CIN. Further studies are necessary to show the exact place of BMP 7 in the recovery period of AKI and whether it might be effective for the treatment of this clinical condition or not, since the mortality and morbidity rates of AKI and CIN are still so high.

Conflict of interest statement. None declared.

1Department of Internal Medicine Section of Nephrology, Fatih University School of Medicine Ankara, Turkey
2Department of Nephrology Clinic and Dialysis and Transplantation Center, ‘C. I. PARHON’ University Hospital, Iasi, Romania
E-mail: drkanbay@yahoo.com

Advace Access publication 11 November 2009

Bone morphogenic protein-7: a new prognostic marker for acute kidney injury?

Sir,

Bone morphogenic protein-7 (BMP-7), also known as osteogenic protein-1 (OP-1), is one of the members of the transforming growth factor β (TGF-β) superfamily [1]. This protein was originally identified as a regulator of cartilage and bone formation. However, BMPs have also been shown to regulate the growth, differentiation and migration of various cell types, including epithelial, mesenchymal, neuronal and hematopoietic cells [2].

Acute kidney injury (AKI)—characterized by a sudden loss of the ability of the kidneys to excrete nitrogenous waste, and to maintain electrolyte and fluid balance—is a frequently encountered clinical problem, especially in the intensive care unit patients. Despite some advances in the management of this condition, unfortunately the morbidity and mortality rates of established AKI still remain high (30–70%) [3]. Acute renal failure occurs as a result of a sudden decrease in renal blood flow, toxic or obstructive insult to the renal tubule or inflammation in the tubulointerstitium. The subsequent dysfunction and loss of tubular epithelial cells is of key importance for the pathophysiological consequences of the syndrome. Contrast-induced nephropathy (CIN) is a distinct type of AKI. Although the pathophysiological processes of CIN are not completely understood, many potential mechanisms for renal injury have been proposed—including contrast-media-induced vasoconstriction resulting in reduction in renal blood flow, direct tubular toxicity and free radical and oxidative injury to tubular cells [4].

Tubular epithelial cells (TECs) are a major source of chemokines, cytokines (such as interleukin-6) and growth factors (such as tumour necrosis factor-α) and they play an important role in the initiation of interstitial inflammation. Furthermore, TECs contribute to the progression of renal fibrosis by undergoing an epithelial–mesenchymal transition (EMT), and leading to accumulation of activated fibroblasts in the interstitium [5].

Several studies showed that the principal target of BMP-7 in the kidney was TECs [6]. It is also demonstrated that BMP-7 decreases the secretion of pro-inflammatory cytokines and growth factors by TECs and reverses epithelial-to-mesenchymal transition, while it acts as an antagonist of TGF-β1-induced E-cadherin downregulation [7,8].

Acute kidney injury associated with tubular necrosis leads to reduction in the expression of tubular BMP-7, and after recovery of tubular and glomerular damage, BMP-7 expression is restored [9]. It is demonstrated that BMP-7 can inhibit EMT involving tubular epithelial cells, resulting in potential repair of injured tubules [8]. Furthermore, administration of exogenous rhBMP-7 accelerates the repair of the injured kidney in animal models [10]. Those findings suggest that BMP-7 plays a critical role in the maintenance of kidney homeostasis [9].

In summary, these data suggest that BMP-7 is an important regulator of the tubular epithelial cell function, inflammatory response and epithelial–mesenchymal transition. Reduced expression of BMP-7 may contribute to the fibrotic response, and its administration may ameliorate renal injury. We speculate that by potential mechanisms of repairing injured tubules, BMP-7 has a critical role in recovery of AKI and it may have a prognostic value. Measuring BMP-7 levels might predict the development of CIN and administering rhBMP-7 to high-risk groups (such as predisposed subjects to CIN, requiring contrast investigations) might prevent the development of CIN. Further studies are necessary to show the exact place of BMP 7 in the recovery period of AKI and whether it might be effective for the treatment of this clinical condition or not, since the mortality and morbidity rates of AKI and CIN are still so high.

Conflict of interest statement. None declared.

1Department of Internal Medicine Section of Nephrology, Fatih University School of Medicine Ankara, Turkey
2Department of Nephrology Clinic and Dialysis and Transplantation Center, ‘C. I. PARHON’ University Hospital, Iasi, Romania
E-mail: drkanbay@yahoo.com