Polyarteritis Nodosa-Associated with IgA Nephropathy – Case Report and Literature Review

Wei Lin¹, Hsin-Fan Chen¹, I-Wen Wu¹, Yeon-Jian Jan Wu², and Mai-Szu Wu¹

¹School of Medicine, Chang Gung University; Division of Nephrology
²Division of Rheumatology
Chang Gung Memorial Hospital, Keelung, Taiwan, Republic of China

Abstract

Polyarteritis nodosa (PAN)-associated glomerulonephritis presenting with nephrotic syndrome is not common. We describe a 69-year-old hypertensive man in whom PAN coexisted with IgA nephropathy presenting with severe nephrotic syndrome, livedo reticularis, testicular pain, and microaneurysm of renal vessels. Extensive literature review of PAN-associated glomerulonephritis was summarized. PAN-associated IgA nephropathy should be considered in a patient having PAN with nephrotic syndrome. Steroid therapy is an effective therapy in cases where these 2 diseases coexisted.

KEY WORDS: glomerulonephritis, IgA nephropathy, nephrotic syndrome, polyarteritis nodosa

Case Report

Corresponding author: Mai-Szu Wu, M.D., Division of Nephrology, Chang Gung Memorial Hospital, No. 222, Mai-Chin Rd., Keelung, Taiwan, R.O.C. Tel: +886-2-24313131 ext. 3169, Fax: +886-2-24335342, E-mail: maxwu1@adm.cgmh.org.tw

Received: March 21, 2011; Revised: May 16, 2011; Accepted: September 28, 2011.

Introduction

Polyarteritis nodosa (PAN), first described by Kussmaul and Maier in 1866, is an uncommon systemic necrotizing vasculitis and is characterized by inflammatory reactions of medium-sized muscular arteries, which lead to aneurysm formation with the involvement of multiple organs, including skin, kidneys, peripheral nerves, muscles, and gastrointestinal tract (1). The clinical features are tissue infarction, hemorrhage, and organ dysfunction (2). Renal involvement of PAN is frequent and constitutes 93.4% of all visceral manifestations (3). Common renal manifestations include loin pain and hematuria due to renal infarction, renal dysfunction, and renin-dependent hypertension secondary to ischemia, microaneurysm of renal vasculature, perirenal hematoma because of microaneurysm rupture (2), and bilateral reversible hydronephrosis (4, 5).

PAN-associated glomerulonephritis presenting with nephrotic syndrome is not common. Some investigators have described the association of PAN with cryoglobulinemic glomerulonephritis (6) hepatitis B virus-related membranous nephropathy (7) antiglomerular basement membrane disease (7); Berger disease (8) and in particular, the Henoch-Schonlein purpura (HSP) (9, 10). All these cases manifested with hematuria and/or non-nephrotic-range proteinuria. Herein, we describe a patient with PAN presenting with nephrotic syndrome; renal biopsy for this patient revealed IgA nephropathy.

Case Report

A 69-year-old hypertensive man was admitted because of diffuse skin lesions and bilateral leg edema for 1 week. There was no fever, itching, swelling, local heat, or tenderness. The patient complained of testicular pain and livedo reticularis was observed. On admission, the blood pressure was 144/93 mmHg; respiratory rate, 12; heart beat, 99/min; and temperature, 36.5°C. Physical examination revealed diffuse purpuric plaque, with necrotic change over the lower limbs, which extended into the trunk and upper limbs. Both legs also had pitting edema over the pretibial and pedal areas. The auscultation of the lungs and
heart was normal. No lymphoadenopathy, hepato-, or splenomegaly was found. The patient had a medical history of ruptured anterior communicating artery aneurysm and right carotid artery stenosis. He had also undergone a ventriculo-peritoneal shunt for normal pressure hydrocephalus. The patient received aspirin for secondary prevention of old ischemic stroke since September, 2000. The patient did not receive any ACEI or ARB. He denied having received any new medication or herbal medicine.

Laboratory findings showed that the hemoglobin level was 12.3 g/dL; hematocrit value, 37.8%; white cell count, 6,200/mm³ (differential count: 74.8% neutrophils, 20.3% lymphocytes, 4.2% monocytes); and platelet count, 260,000/mm³. The erythrocyte sedimentation rate (ESR) was 31 mm/h. Serum electrolyte (sodium, potassium, calcium, and phosphate), amylase, lipase, and blood glucose levels were normal; the creatinine level was 0.9 mg/dL and urea nitrogen was 8 mg/dL. The albumin level was 2.5 g/dL; globulin, 1.9 g/dL; total cholesterol, 206 mg/dL; and triglyceride, 102 mg/dL.

Anti-nuclear antibody (ANA) titer was 1:40 (weakly positive). The C3 level was 140 mg/dL (normal 73-134 mg/dL) and the C4 level was 20.3 mg/dL (normal, 18.2-45.5 mg/dL). The serum concentrations of the antibodies were as follows: IgG, 885.0 mg/dL; IgA, 121.0 mg/dL; IgM, 88.4 mg/dL; and IgE, < 1.50 IU/mL. Urinalysis showed proteinuria (500 mg/dL), hematuria (blood: 3+), and 61-70 erythrocytes in each high-power field. In a 24-h specimen of urine, the amount of protein was 5.6 g. Nephrotic syndrome is impressed. Antibodies to double-strand DNA and extractable nuclear antigen (ENA), including Smith antigen and cryoglobulins, were absent. The hepatitis B surface antigen (HBsAg) and antibodies against hepatitis C virus (HCV) were absent. The sample was weakly positive for perinuclear anti-neutrophilic cytoplasmic antibodies (P-ANCA) and negative for cytoplasmic anti-neutrophilic cytoplasmic antibodies (C-ANCA) and anti-cardiolipin antibodies.

Skin biopsy revealed abundant neutrophil infiltrates around medium-sized dermal vessels with fibrinoid necrosis, hemorrhage, and nuclear dusts, which was consistent with features of necrotizing vasculitis (Fig. 1A). Study of skin biopsy by direct immunofluorescence showed negative findings. Percutaneous renal biopsy was performed and light microscopy showed mild mesangial hyperplasia with interstitial fibrosis. The tubules contained protein casts. Arterioles and capillaries had a normal appearance (Fig. 1B). An immunofluorescence study revealed marked granular deposits of IgA and C3 in the mesangium (Fig. 1C), indicating IgA nephropathy. Computed-tomographic angiography disclosed irregular caliber and multiple narrowing in the segmental and interlobar arteries of both kidneys (Fig. 2).

The patient received pulse hydrocortisone therapy (400 mg daily, for 5 days), followed by oral pred-
nisolone 80 mg daily, which was then tapered to 50 mg daily. The skin lesions, edema, and proteinuria regressed rapidly after steroid therapy. The follow-up at outpatient clinic revealed that the patient was negative for proteinuria.

**Discussion and Review of Literature**

The clinical constellation of the patient included nephrotic syndrome, livedo reticularis, testicular pain, diastolic BP of above 90 mmHg, necrotizing vasculitis of medium-sized dermal vessels, and microaneurysm formation of segmental and interlobar arteries of both kidneys. PAN is conclusively diagnosed if 5 out of the 10 American College of Rheumatology (ACR) criteria are fulfilled (11).

Nephrotic syndrome is rarely associated with PAN. The renal histology of classic PAN comprises fibrinoid necrosis of arcuate or interlobular arteries with marked inflammatory response within and surrounding a vessel (12). The renal manifestation of PAN often presents as hematuria and hypertension. However, the renal specimen of our patient revealed normal arterioles and capillaries and marked IgA deposition in the mesangium. This microscopic picture suggested the coexistence of IgA nephropathy in this PAN patient. The skin biopsy revealed medium-sized vessel with fibrinoid necrosis; however, it was negative for IgA staining. Furthermore, the dermal vasculitis may come from PAN rather than IgA nephropathy. Mesangial deposit of IgA in PAN patients has been reported in the literature, and all the cases in the literature had hematuria or non-nephrotic-range proteinuria at presentation. The presence of nephrotic syndrome in our patient is peculiar. Praderio et al. (8) first described the causal relationship between IgA nephropathy and PAN. Subsequently, other authors described fatal cases of PAN associated with HSP (9, 10, 13, 14) and termed this condition as polyangiitis overlap syndrome (15). Literature review revealed a few cases of PAN associated-glomerulonephritis. The proteinuria in all cases was mild, and the outcome of these cases was dismal (Table 1). Coexistence of PAN and IgA nephropathy has rarely been reported in the literature. The exact mechanism for this association is unclear. IgA nephropathy is associated with prominent, globular deposits of IgA (often accompanied by C3 and IgG) in the mesangium but also, to a lesser degree, along the glomerular capillary wall. A possible explanation for the heavy proteinuria of our patient is the possible glomerular capillary or podocytes involvement. Electron microscopy in IgA nephropathy typically reveals electron-dense deposits that are primarily limited to the mesangium but may also occur in the subendothelial and subepithelial spaces. Electron microscopy may add additional information but is lacking in our patient.

The association of IgA nephropathy with HSP is particularly strong, and the two diseases may actually share the same mechanism of pathogenesis. In view of the absence of gastrointestinal and musculoskeletal manifestation and negative immunoglobulin deposition on the skin biopsy of our patient, we thought that HSP was an unlikely diagnosis. Praderio et al. (8) described a patient with a past infection with hepatitis B virus (HBV) who presented with gross hematuria and a mild proteinuria of 0.6 g/day. The patient responded successfully to prednisolone therapy. It was thus concluded that the circulating immune complex might have a pathogenic role in the development of systemic vasculitis. Whether the presence of the HBV marker could trigger immune complex formation in such patients remains unknown. The serology of our patient was negative for hepatitis B infection. The pathogenic mechanism of IgA nephropathy involved mesangial precipitation of the circulating immune complex with altered O-glycosylation of serum IgA1 (16). In contrast, confocal microscopy analysis revealed a direct deposition of undergalactosylated IgA1 in the mesangium independent of the immune complex formation (17). It is possible that the immune complex formation in PAN may contain aberrant IgA that precipitates in the mesangium. However, the exact mechanism eliciting abnormal IgA glycosylation in PAN patients remains unclear.

The outcome of PAN-associated glomerulonephritis is poor (9, 10, 13, 14). Glucocorticoid ther-
### Table 1. Glomerulonephritis associated with PAN: a literature review

<table>
<thead>
<tr>
<th>Case</th>
<th>Author</th>
<th>Year</th>
<th>Glomerulonephritis</th>
<th>Age</th>
<th>Gender</th>
<th>Initial presentation</th>
<th>Renal presentation</th>
<th>HBVsAg</th>
<th>ANCA</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Praderio (8)</td>
<td>1989</td>
<td>IgAN</td>
<td>17</td>
<td>M</td>
<td>Intermittent claudication</td>
<td>Gross hematuria</td>
<td>N</td>
<td>NA</td>
<td>Steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>Kirkland (7)</td>
<td>1996</td>
<td>Anti-GBM disease</td>
<td>72</td>
<td>F</td>
<td>Diarrhea, abdominal pain, fever</td>
<td>Proteinuria, hematuria</td>
<td>NA</td>
<td>N</td>
<td>Cyclophosphamide + steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>Mouthon (20)</td>
<td>1995</td>
<td>MGN</td>
<td>70</td>
<td>M</td>
<td>Weight loss, arthralgias, myalgias</td>
<td>Nephrotic syndrome</td>
<td>P</td>
<td>N</td>
<td>Plasmapheresis + IFN α</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>Yokose (14)</td>
<td>1993</td>
<td>HSP</td>
<td>77</td>
<td>M</td>
<td>Leg skin eruptions</td>
<td>Proteinuria, hematuria</td>
<td>N</td>
<td>NA</td>
<td>Pulse steroid</td>
<td>Dead</td>
</tr>
<tr>
<td>5</td>
<td>Birchmore (13)</td>
<td>1996</td>
<td>HSP</td>
<td>50</td>
<td>M</td>
<td>Purpuric rash, abdominal pain, arthralgia, myalgia</td>
<td>Proteinuria, hematuria</td>
<td>NA</td>
<td>N</td>
<td>Cyclophosphamide + steroid</td>
<td>Dead</td>
</tr>
<tr>
<td>6</td>
<td>Cnada (6)</td>
<td>2006</td>
<td>Cryoglobulinemic GN</td>
<td>53</td>
<td>M</td>
<td>Hypertensive encephalopathy, purpuric lesions</td>
<td>Proteinuria, hematuria</td>
<td>N</td>
<td>N</td>
<td>Cyclophosphamide + steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>7</td>
<td>Leavitt (15)</td>
<td>1986</td>
<td>Churg-Strauss</td>
<td>21</td>
<td>M</td>
<td>NA</td>
<td>Microaneurysm</td>
<td>N</td>
<td>NA</td>
<td>Cyclophosphamide + steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>8</td>
<td>Leavitt (15)</td>
<td>1986</td>
<td>Vasculitis</td>
<td>54</td>
<td>F</td>
<td>NA</td>
<td>Microaneurysm</td>
<td>N</td>
<td>NA</td>
<td>Cyclophosphamide + steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>Leavitt (15)</td>
<td>1986</td>
<td>HSP</td>
<td>33</td>
<td>M</td>
<td>NA</td>
<td>Vasculitis</td>
<td>N</td>
<td>NA</td>
<td>Cyclophosphamide + steroid</td>
<td>Alive</td>
</tr>
<tr>
<td>10</td>
<td>Watanabe (9)</td>
<td>2003</td>
<td>HSP</td>
<td>56</td>
<td>M</td>
<td>Arthralgia, purpura, nasal bleeding, tarry stool</td>
<td>Proteinuria, hematuria</td>
<td>N</td>
<td>N</td>
<td>Hemodialysis</td>
<td>Dead</td>
</tr>
<tr>
<td>11</td>
<td>Lin</td>
<td>2010</td>
<td>IgAN</td>
<td>69</td>
<td>M</td>
<td>Purpuric lesions</td>
<td>Nephrotic syndrome</td>
<td>N</td>
<td>p-ANCA</td>
<td>Steroid</td>
<td>Alive</td>
</tr>
</tbody>
</table>

Abbreviations: P-ANCA, perinuclear anti-neutrophilic cytoplasmic antibodies; Anti-GBM, anti-glomerular basement membrane; GN, glomerulonephritis; y, years-old; M, male; F, female; P, positive; N, negative; NA, not available; IFNα, interferon alpha; HSP, Henoch-Schonlein Purpura; IgAN, IgA nephropathy; MGN, membranous nephropathy.
apy is beneficial in most patients with PAN (18, 19). However, a cytotoxic agent should be used in most cases when PAN coexists with vasculitis. In contrast, the results of Praderio (8) and our patient demonstrated that predisolone therapy alone was effective for PAN-associated IgA nephropathy.

In conclusion, we found a patient with concurrent IgA nephropathy and PAN. Steroid therapy is an effective therapy in cases where these two diseases coexisted.

References