Acute Kidney Injury in a Patient with Polyarteritis Nodosa and Multiple Myeloma

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Abstract

We herein report the case of a Japanese man with polyarteritis nodosa (PAN) accompanied by multiple myeloma (MM). The patient was diagnosed with PAN. Concurrently, IgG kappa paraprotein was detected, and bone marrow changes indicative of MM were observed. Prednisolone (PSL) administered at a dose of 30 mg/day was initiated; however, the serum creatinine level increased. In spite of increasing the dose of PSL to 45 mg/day and initiating treatment with double filtration plasmapheresis, the patient’s renal dysfunction continued to progress and haemodialysis was introduced. He died from pneumonia 12 months after admission. We conclude that renal failure is an important risk factor in the prognosis of PAN accompanied by MM.

Key words: acute kidney injury, polyarteritis nodosa, multiple myeloma, double filtration plasmapheresis


Introduction

Polyarteritis nodosa (PAN) is a form of necrotizing arteritis of small- and medium-sized muscular arteries with multiple organ involvement. PAN is rarely complicated by acute kidney injury (AKI) in patients with renal involvement (1). Multiple myeloma (MM) is a disease characterized by the malignant proliferation of plasma cells from a single clone. MM-associated blood hyperviscosity sometimes induces renal disease, which progresses to renal insufficiency (2-5). We herein report the case of a patient with PAN accompanied by MM and AKI. We also describe the relationship between PAN and MM as well as important risk factors for the prognosis of PAN complicated by MM.

Case Report

A 58-year-old Japanese man was admitted to our hospital due to a 4-month history of a low-grade fever, body weight loss, weakness in the legs and polyarthralgia. On admission, he was febrile (37.9°C), his body weight (BW) was 41 kg and his blood pressure was 100/60 mmHg. The palpebral conjunctiva appeared anaemic, although no marked headaches, dizziness, backaches or hemorrhage were observed. A physical examination showed muscle weakness in the legs, livedo reticularis in the lower part of the legs and no changes in the fundus oculi. The results of laboratory examinations were as follows: white blood cell count 8,320/μL, haemoglobin 8.9 g/dL, platelet count 455,000/μL and erythrocyte sedimentation rate >140 mm/h. The serum concentration of total protein was 9.4 g/dL, the albumin level was 2.4 g/dL, the albumin level was 4.978 mg/dL, the IgA level was 53 mg/dL, the IgM level was 29 mg/dL, the C-reactive protein level was 11.6 mg/dL, the serum creatinine (sCr) level was 2.4 mg/dL, the IgG level was 4,978 mg/dL, the IgA level was 53 mg/dL, the IgM level was 29 mg/dL, the C-reactive protein level was 11.6 mg/dL, the serum creatinine (sCr) level was 64.6 μmol/L and the calcium level was 2.17 mmol/L. The results of tests for rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, cryoglobulin, circulating immune complex, hepatitis B surface antigens and hepatitis C virus antibodies were all negative, and the levels of serum C3 and C4 were normal. The results of a urinalysis were normal, with no Bence Jones protein (BJP) or sediment. Electrophoresis of serum proteins showed a monoclonal spike in the gamma region, which was characterized as the IgG kappa chain on serum immunoelectrophoresis. Roentgenograms of the chest and skeleton...
were normal. The results of a biopsy of the skin obtained from the lower part of the patient’s leg indicated fibrinoid necrosis of the medium and small arteries, indicative of a PAN diagnosis (Fig. 1A and B). A bone marrow biopsy showed more than 70% atypical plasma-like cells, which confirmed the diagnosis of MM (Fig. 1C). No treatment for the myeloma was administered because the disease was completely asymptomatic (i.e. there was a paraprotein and abnormal bone marrow population but no end-organ damage), as observed in patients with smoldering myeloma.

On the 40th day of hospitalization, the patient was treated for PAN with prednisolone (PSL) at a dose of 30 mg/day. After three weeks, however, the sCr level gradually became elevated to 123.9 μmol/L, and the PSL dose was increased to 45 mg/day based on the PAN diagnosis. Two weeks later, the sCr level had increased to 177.0 μmol/L. A renal biopsy was performed, and diffuse tubular atrophy together with severe interstitial fibrosis and marked inflammatory mononuclear cell infiltration were observed (Fig. 2A). The glomerular capillaries were occupied by red blood cells, suggesting hypoperfusion of the glomeruli (Fig. 2B). The arcuate arteries showed destruction of the elastic lamina with inflammatory cell infiltration, indicating fibrinoid necrosis (Fig. 2C and D). Otherwise, the glomeruli exhibited almost normal findings without any proliferation or deposition. Direct immunofluorescence staining for C3, C4, IgG, IgA, IgM and kappa and lambda light chains revealed no significant deposition in either the glomeruli or tubules. In addition, Congo red staining demonstrated no amyloid deposition in the renal specimens. These findings indicated the presence of PAN accompanied by severe chronic tubulointerstitial nephritis and glomerular hypoperfusion. Despite the administration of glucocorticoids, the patient’s renal insufficiency worsened and he developed herpes zoster virus and bacterial infections. Instead of immunosuppressive drugs, he received double filtration plasmapheresis (DFPP) once a week for three weeks for paraproteinemia. The sCr level stabilized for a period of time in association with a decreased paraprotein level; however, unfortunately, the renal dysfunction later recurred due to dehydration and drug-related renal toxicity, and haemodialysis was finally introduced (Fig. 3). The patient ultimately died from severe pneumonia at another hospital 12 months after admission.

**Discussion**

The association between vasculitis and malignancy is well known. It has been estimated that approximately 5% of patients with some form of vasculitis may have a pathogenically related malignancy (6). The common vasculitis phenotypes associated with malignancies include cutaneous vasculitis and PAN (6). Hutson et al. investigated 12 patients with vasculitis complicated by cancer and reported that six patients had solid organ tumors, four had lymphomas, one had...
Figure 2. Renal biopsy specimen showing diffuse tubular atrophy, interstitial fibrosis, inflammatory mononuclear cell infiltration and glomerular capillaries obstructed by red blood cells (A: Hematoxylin and Eosin staining: objective lens, ×10, B: ×40). The arcuate artery exhibits fibrinoid necrosis surrounded by inflammatory cell infiltration (C: Elastica van Gieson stain: objective lens, ×10, D: ×40).

Figure 3. The sCr and IgG levels and therapy during hospitalization. sCr: serum creatinine, DFPP: double filtration plasmapheresis, HD: haemodialysis, PSL: prednisolone
leukemia and one had MM (7). Vasculitis is rarely accompanied by MM. To the best of our knowledge, nine cases of PAN with a complication of MM, including our case, have been reported (7-14) (Table). The reports show that the mean age of these patients was 54.3 years (range, 37-78 years). Seven of the nine patients were men. Moreover, seven of the nine patients were diagnosed within three months after developing PAN and MM. Four of the nine patients had IgA kappa MM, one had IgG kappa MM and one had IgG lambda MM; however, data for the other three patients were not available. The most common pathological finding on renal biopsies was fibrinoid necrosis of the arterial wall of small- and medium-sized vessels, which occurred in four patients. In five of the nine patients, progression to end-stage renal failure was observed, and all of these patients died. Therefore, we suggest that renal failure is an important risk factor in the prognosis of PAN accompanied by MM.

The role of plasmapheresis in the management of renal failure in MM patients has been explored in three randomized controlled trials; however, the potential advantage of this treatment remains controversial (15-17). In our case, a renal biopsy did not show any typical renal pathological alterations associated with paraproteinemia, e.g., cast nephropathy, amyloidosis or deposition disease. Moreover, as described above, the patient’s urine was negative for BJP and no cryoglobulinemia was detected. On the other hand, there are a few reports showing monoclonal gammopathy-associated renal impairment without paraprotein deposition in either the glomeruli or tubules (18-24). In a case series of nine patients, Ramos et al. concluded that the presence of paraproteins may lead to secondary renal impairment, and they reported four patients who exhibited a worsening of the renal function and required dialysis during a mean follow-up period of 2.4±4.3 years (25). Therefore, we concluded that the major pathological mechanism in our patient was the presence of hyperviscosity due to paraproteins. It is reasonable to assume that PAN caused hypoperfusion of the glomeruli and peritubular capillaries and that chronic hypoxia in the kidneys resulted in tubulointerstitial alterations with severe fibrosis. In addition, the glomerular capillaries were occupied by red blood cells, thus suggesting hyperviscosity of paraproteins, which may have caused a deterioration of the PAN-associated hypoperfusion of the glomeruli and peritubular capillaries, thereby resulting in AKI. Additionally, glucocorticoid monotherapy may have affected the hyperviscosity to some extent. For this reason, we performed DFPP, instead of total plasma exchange, once a week for three weeks and found that it actually reduced the amount of IgG. The patient had refused haemodialysis during this period. Our literature search found that this is the first report to describe the short-term efficacy of DFPP in the treatment of corticosteroid-refractory PAN associated with MM. We recommend that, in patients with PAN, MM and complicating infectious diseases, DFPP is an alternative treatment until the induction of haemodialysis.

Concerning the treatment of PAN and MM, vasculitis and malignancies exhibit a temporal relationship, similar to a paraneoplastic condition. In fact, Hutson et al. reported that eight of 12 patients with vasculitis and cancer demonstrated marked improvements in vasculitis upon treatment of the associated malignancy (7). Although we did not administer chemotherapy when MM was diagnosed because the disease was completely asymptomatic and no evidence of end-organ damage was observed, dexamethasone-based chemotherapy (e.g. bortezomib and dexamethasone) may have been alternatively selected for MM in this patient.

In conclusion, we herein reported the case of a patient with overlapping PAN and MM with a very poor prognosis. It is important to perform earlier renal biopsies in order to understand and predict the patient’s renal condition, and, once the diagnosis of PAN associated with MM is made, a

### Table. Case Reports of Polyarteritis Nodosa with Multiple Myeloma

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>MM type</th>
<th>Renal biopsy</th>
<th>Therapy</th>
<th>Progress to renal failure</th>
<th>Outcome</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>53</td>
<td>male</td>
<td>- a</td>
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<td>Stilbamidine</td>
<td>(-)</td>
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<td>(8)</td>
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<tr>
<td>47</td>
<td>female</td>
<td>- a</td>
<td>vasculitis</td>
<td>Steroid</td>
<td>(+)</td>
<td>dead</td>
<td>(13)</td>
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<tr>
<td>51</td>
<td>male</td>
<td>IgA k</td>
<td>renal infarction</td>
<td>Steroid, AZA, CY, PE</td>
<td>(+)</td>
<td>dead</td>
<td>(14)</td>
</tr>
<tr>
<td>37</td>
<td>male</td>
<td>IgG k</td>
<td>- a</td>
<td>Steroid, HD, Melphalan</td>
<td>(+)</td>
<td>dead</td>
<td>(10)</td>
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<tr>
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<td>male</td>
<td>IgA k</td>
<td>vasculitis, cast nephropathy</td>
<td>Steroid, CY, HD, Danazol</td>
<td>(+)</td>
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<td>(9)</td>
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<tr>
<td>78</td>
<td>female</td>
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<td>Steroid</td>
<td>(-)</td>
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<td>(12)</td>
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<tr>
<td>59</td>
<td>male</td>
<td>- a</td>
<td>- a</td>
<td>Steroid, CY</td>
<td>(-)</td>
<td>alive</td>
<td>(7)</td>
</tr>
<tr>
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<td>IgA k</td>
<td>- a</td>
<td>Steroid, AZA, CY, Bortezomib, Thalidomide</td>
<td>(+)</td>
<td>alive</td>
<td>(11)</td>
</tr>
<tr>
<td>59</td>
<td>male</td>
<td>IgG k</td>
<td>vasculitis</td>
<td>Steroid, DFPP</td>
<td>(+)</td>
<td>dead</td>
<td>our case</td>
</tr>
</tbody>
</table>

* indicates not described. AZA: azathioprine, CY: cyclophosphamide, PE: plasma exchange, HD: haemodialysis, DFPP: double filtration plasmapheresis
combination of corticosteroids with immunosuppressive drugs and plasmapheresis may be promptly considered.

The authors state that they have no Conflict of Interest (COI).

References


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