□ CASE REPORT □

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

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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/ μ L, haemoglobin 8.9 g/dL, platelet count 455,000/ μ L 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 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 μ mol/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

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Figure 1. Skin biopsy showing a small artery with circular fibrinoid necrosis surrounded by an infiltrate of inflammatory cells (A: Hematoxylin and Eosin staining: objective lens, $\times 10$, B: $\times 40$). Bone marrow aspiration showing atypical plasma-like cells (C: May-Giemsa stain: objective lens, $\times 100$).

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 $\mu\text{mol/L}$, 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 $\mu\text{mol/L}$. 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 signifi-

cant 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

Table. Case Reports of Polyarteritis Nodosa with Multiple Myeloma

Age • Sex	MM type	Renal biopsy	Therapy	Progress to renal failure	Outcome	Reference
53 • male	- *	vasculitis	Stilbamidine	(-)	dead	(8)
47 • female	- *	vasculitis	Steroid	(+)	dead	(13)
51 • male	IgA κ	renal infarction	Steroid, AZA, CY, PE	(+)	dead	(14)
37 • male	IgG λ	- *	Steroid, HD, Melphalan	(+)	dead	(10)
50 • male	IgA κ	vasculitis, cast nephropathy	Steroid, CY, HD, Danazol	(+)	dead	(9)
78 • female	IgA κ	- *	Steroid	(-)	alive	(12)
59 • male	- *	- *	Steroid, CY	(-)	alive	(7)
55 • male	IgA κ	- *	Steroid, AZA, CY, Bortezomib, Thalidomide	(-)	alive	(11)
59 • male	IgG κ	vasculitis	Steroid, DFPP	(+)	dead	our case

*indicates not described. AZA: azathioprine, CY: cyclophosphamide, PE: plasma exchange, HD: haemodialysis, DFPP: double filtration plasmapheresis

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

combination of corticosteroids with immunosuppressive drugs and plasmapheresis may be promptly considered.

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

References

- Samarkos M, Loizou S, Vaiopoulos G, Davies KA. The clinical spectrum of primary renal vasculitis. *Semin Arthritis Rheum* **35**: 95-111, 2005.
- Barosi G, Boccadoro M, Cavo M, et al. Management of multiple myeloma and related-disorders: guidelines from the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES) and Italian Group for Bone Marrow Transplantation (GITMO). *Haematologica* **89**: 717-741, 2004.
- Pillon L, Sweeting RS, Arora A, et al. Approach to acute renal failure in biopsy proven myeloma cast nephropathy: is there still a role for plasmapheresis? *Kidney Int* **74**: 956-961, 2008.
- Sakhuja V, Jha V, Varma S, et al. Renal involvement in multiple myeloma: a 10-year study. *Ren Fail* **22**: 465-477, 2000.
- Hutchison CA, Batuman V, Behrens J, et al. The pathogenesis and diagnosis of acute kidney injury in multiple myeloma. *Nat Rev Nephrol* **8**: 43-51, 2011.
- Hayem G, Gomez MJ, Grossin M, Meyer O, Kahn MF. Systemic vasculitis and epithelioma. A report of three cases with a literature review. *Rev Rhum Engl Ed* **64**: 816-824, 1997.
- Hutson TE, Hoffman GS. Temporal concurrence of vasculitis and cancer: a report of 12 cases. *Arthritis Care Res* **13**: 417-423, 2000.
- Best WR, Fine G. Periarthritis nodosa and multiple myeloma; report of simultaneous occurrence in a patient receiving stilbamidine. *Ann Intern Med* **34**: 1472-1483, 1951.
- Birchmore D, Sweeney C, Choudhury D, Konwinski MF, Carnevale K, D'Agati V. IgA multiple myeloma presenting as Henoch-Schonlein purpura/polyarteritis nodosa overlap syndrome. *Arthritis Rheum* **39**: 698-703, 1996.
- Hasegawa H, Ozawa T, Tada N, et al. Multiple myeloma-associated systemic vasculopathy due to crystalglobulin or polyarteritis nodosa. *Arthritis Rheum* **39**: 330-334, 1996.
- Leroy P, Villee C, Lefebvre C, Knoops L. Multiple myeloma-associated polyarteritis nodosa. *Br J Haematol* **149**: 634, 2010.
- Seelen MA, de Meijer PH, Arnoldus EP, van Duinen SG, Meinders AE. A patient with multiple myeloma presenting with severe polyneuropathy caused by necrotizing vasculitis. *Am J Med* **102**: 485-486, 1997.
- Skoog WA, Adams WS. Metabolic balance study of a patient with multiple myeloma treated with dexamethasone. Dexamethasone-induced fatal necrotizing polyarteritis of coronary vessels and kidneys. *Am J Med* **34**: 417-425, 1963.
- Williams AJ, Newland AC, Marsh FP. Acute renal failure with polyarteritis nodosa and multiple myeloma. *Postgrad Med J* **61**: 445-448, 1985.
- Clark WF, Stewart AK, Rock GA, et al. Plasma exchange when myeloma presents as acute renal failure: a randomized, controlled trial. *Ann Intern Med* **143**: 777-784, 2005.
- Johnson WJ, Kyle RA, Pineda AA, O'Brien PC, Holley KE. Treatment of renal failure associated with multiple myeloma. Plasmapheresis, hemodialysis, and chemotherapy. *Arch Intern Med* **150**: 863-869, 1990.
- Zucchelli P, Pasquali S, Cagnoli L, Ferrari G. Controlled plasma exchange trial in acute renal failure due to multiple myeloma. *Kidney Int* **33**: 1175-1180, 1988.
- Kagaya M, Takahashi H. A case of type I cryoglobulinemia associated with a monoclonal gammopathy of undetermined significance (MGUS). *J Dermatol* **32**: 128-131, 2005.
- Ma CX, Lacy MQ, Rompala JF, et al. Acquired Fanconi syndrome is an indolent disorder in the absence of overt multiple myeloma. *Blood* **104**: 40-42, 2004.
- Hashimoto T, Arakawa K, Ohta Y, et al. Acquired fanconi syndrome with osteomalacia secondary to monoclonal gammopathy of undetermined significance. *Intern Med* **46**: 241-245, 2007.
- Kobayashi T, Muto S, Nemoto J, et al. Fanconi's syndrome and distal (type 1) renal tubular acidosis in a patient with primary Sjögren's syndrome with monoclonal gammopathy of undetermined significance. *Clin Nephrol* **65**: 427-432, 2006.
- Nagao T, Okura T, Miyoshi K, et al. Fibrillary glomerulonephritis associated with monoclonal gammopathy of undetermined significance showing lambda-type Bence Jones protein. *Clin Exp Nephrol* **9**: 247-251, 2005.
- Hii IM, Chen ML, Chang CC. Benign monoclonal gammopathy-associated acute kidney injury: case report and literature review. *Ren Fail* **32**: 636-638, 2010.
- Parry HM, Pratt G, Hutchison CA. Monoclonal gammopathy of undetermined significance: an update for nephrologists. *Adv Chronic Kidney Dis* **19**: 291-296, 2012.
- Ramos R, Poveda R, Bernis C, et al. Renal involvement in benign monoclonal gammopathies: an underdiagnosed condition. *Nefrologia* **28**: 525-529, 2008.