AP-VAS 2012 case report: a case of systemic MPO-ANCA-associated vasculitis that demonstrated brain infarction and immunohistochemically MPO-positive capillaries

Atsushi Kurata · Satoko Kawashima · Yuichi Terado · Yoshinori Komagata ·
Shinya Kaname · Haruko Okano · Kazutoshi Nishiyama · Kazuhiko Hirano ·
Hiroshi Kamma · Yoshihiro Arimura · Akira Yamada

Received: 11 September 2012 / Accepted: 25 November 2012 / Published online: 13 February 2013
© Japanese Society of Nephrology 2013

Abstract We present a case of an aged male with myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA)-associated vasculitis with onset of brain infarction that demonstrated immunohistochemically MPO-positive capillaries at autopsy. The patient initially presented with gait difficulty and right-sided weakness. Since an imaging study revealed brain infarction, he was admitted to our hospital and medicated by antiplatelet agents. Continuous fever and elevated serum C-reactive protein (CRP), hematuria of glomerular origin, renal dysfunction, and high serum titer of MPO-ANCA were detected. Systemic toxicoderma appeared, and skin biopsy revealed small-vessel vasculitis; thus, he was diagnosed with MPO-ANCA-associated vasculitis. Steroid therapy (methylprednisolone 30 mg/day) was started, and general status improved. However, he died of shock 6 days after the start of the therapy. Autopsy revealed massive retroperitoneal hemorrhage with necrotizing small-vessel vasculitis in systemic organs including retroperitoneum, skin, brain, testes, and kidneys. Immunohistochemically,

infiltration of MPO-positive white blood cells into the capillaries was occasionally observed, along with the features of MPO-positive capillaries. Cerebrovascular involvement of MPO-ANCA-associated vasculitis is rare compared with renal and pulmonary manifestations, having been reported to occur in up to 4 % of patients. Furthermore, as we have recently reported, MPO-immunopositive capillaries may appear only during the hyperacute stage of the disease. Therefore, the present case represents the unique combination of these two rare manifestations.

Keywords MPO-ANCA · Vasculitis · Immunohistochemistry · Brain · Autopsy

Introduction

Myeloperoxidase anti-neutrophil cytoplasmic autoantibody (MPO-ANCA)-associated vasculitis is histologically characterized by necrotizing capillaritis in the involved organs [1]. Although respiratory and renal involvements are common [1], cerebrovascular involvement is rare, accounting for up to 4 % [1–3]. Furthermore, histological documentation of brain in this disease is extremely rare. On the other hand, the etiology of the capillaritis has been postulated to be the release of enzymes including MPO from neutrophils, which are activated by ANCA and cytokines, also known as the ANCA-cytokine sequence theory [4, 5]. However, immunohistochemical detection of MPO-positive cells on the capillary has rarely been reported. We have recently demonstrated immunohistochemically that MPO-positive cells do infiltrate into the capillary as well as the presence of MPO on the capillary wall of the glomeruli and pleura in the early stage of MPO-ANCA-associated nephritis and vasculitis, and postulated

A. Kurata (✉)
Department of Molecular Pathology, Tokyo Medical University,
6-1-1 Shinjuku, Shinjuku-ku, Tokyo 160-8402, Japan
e-mail: akurata@tokyo-med.ac.jp

S. Kawashima · Y. Komagata · S. Kaname · Y. Arimura ·
A. Yamada
First Department of Internal Medicine, Kyorin University School
of Medicine, Tokyo, Japan

Y. Terado · K. Hirano · H. Kamma
Department of Pathology, Kyorin University School
of Medicine, Tokyo, Japan

H. Okano · K. Nishiyama
Stroke Center, Kyorin University Hospital, Tokyo, Japan

that this phenomenon is observed in only the hyperacute stage of the disease [6, 7]. Here, we present an autopsy case of the rare occurrence of MPO-ANCA-associated vasculitis with cerebrovascular involvement along with detailed histopathological evaluations including MPO-positive cells in the capillary.

Case report

An 82-year-old Japanese male is presented. His past history included hypertension and unstable angina since he was 61 years old and percutaneous transluminal coronary angioplasty performed when he was 71 years old. He was a nonsmoker and social drinker, and there was no patient with collagen disease in his family and relatives. His daily medicines were aspirin 100 mg, amlodipine besylate (calcium channel blocker) 10 mg, and metoprolol tartrate (beta-blocker) 60 mg.

On July 20th, general malaise and weakness of lower extremity with gait difficulty appeared and gradually worsened. On August 4th, he was diagnosed with brain infarction (left corona radiata region) by an imaging study (Fig. 1), and admitted to the stroke center. Although the paralysis was stabilized by medication with antiplatelet agents, low-grade fever and elevated serum C-reactive protein (CRP) (10–15 mg/dl) continued despite the prescription of antibiotics. Hematuria of glomerular origin, renal dysfunction (creatinine: elevation from 1.0 to 3.1 mg/dl), and high serum titer of MPO-ANCA (130 EU) were detected; therefore, ANCA-associated vasculitis was

suspected, and he was admitted to internal medicine on August 18th.

At the time of this admission, on physical examination, his blood pressure was 100/70, with a regular pulse rate of 90 beats/min. His temperature was 37.0 °C. His electrocardiogram was normal (in sinus rhythm) and his echocardiogram was also within normal limits. Hematological and blood chemical values were as follows: white blood cell count $19,300/\text{mm}^3$ (seg. 82.5 %, eosino. 4 %, mono. 2 %, lympho. 11 %), red blood cell count $328 \times 10^4/\text{mm}^3$,

Fig. 2 Purpura is noted in the chest and abdomen

Fig. 1 Head magnetic resonance imaging (MRI) reveals infarct of left corona radiata region (perforating branch)

Fig. 3 Skin biopsy from the left leg shows lymphocytic and neutrophilic infiltration in and around the vessel wall in the deeper dermis

Fig. 4 Diffuse retroperitoneal hemorrhage with hemorrhagic ascites is noted

Fig. 6 Inflammatory infiltrate with focal fibrinoid necrosis in a small artery of the brain

Fig. 5 Inflammatory infiltrate with fibrinoid necrosis in a small artery of the retroperitoneum

hemoglobin 10.5 g/dl, hematocrit 32.9 %, platelet count $17.3 \times 10^4/\text{mm}^3$, total bilirubin 1.4 mg/dl, aspartate aminotransferase 36 IU/l, alanine aminotransferase 22 IU/l, alkaline phosphatase 559 IU/l, γ -glutamyltranspeptidase 35 IU/l, urea nitrogen 62.5 mg/dl, creatinine 3.1 mg/dl, CRP 14.4 mg/dl, and total serum protein 5.6 g/dl (albumin 1.6 g/dl). Urinary protein was negative, and occult blood was 2+ (sediments: protein 0.2 g/dl, RBC 5–9/HPF).

As generalized rash appeared (Fig. 2), skin biopsy from the left leg was performed. The histology revealed small-vessel vasculitis in the deeper dermis (Fig. 3); thus, he was diagnosed with MPO-ANCA-associated microscopic polyangiitis (MPA). Steroid therapy (methylprednisolone 30 mg/day) was started, and general status improved. Although CRP rapidly reduced from 14.4 to 4.1 mg/dl in several days, renal dysfunction progressed as revealed by

Fig. 7 Infiltration and penetration of MPO-positive cells (red) into endothelium of a small cerebral artery

increased serum creatinine level from 3.1 to 4.9 mg/dl. Six days after the start of the therapy, he complained of abdominal discomfort and lumbar pain, and suddenly died of shock.

Autopsy was performed 13 h after death. Thoracotomy and laparotomy revealed hemorrhagic pleural effusions (lt. 450 ml, rt. small amount) and ascites (160 ml) as well as diffuse retroperitoneal hemorrhage (Fig. 4). Histologically, multiple necrotizing vasculitis in small and medium-sized arteries were confirmed in the retroperitoneum (Fig. 5) and

Table 1 Cerebrovascular involvement in patients with MPO-ANCA-associated vasculitis

No.	First author	Reference	Year	Age	Sex	Cerebrovascular lesion	Lung	Kidney	Other organ involvement	MPO-ANCA (EU)	Pathology	Therapy	Outcome
1	Sasaki	[8]	1998	78	M	Infarct	Hemorrhage, IP	RPGN	GI bleeding	637	MPA (brain)	Not done	Died
2	Deshpande	[9]	2000	15	F	Ischemia	Edema	RPGN	(–)	26	(–)	PSL, CPA, IVCY, PE, CAPD	Improved
3	Saito	[10]	2003	57	F	Hemorrhage	Hemorrhage	RPGN	DIC, GI bleeding	765	(–)	PSL, CPA, PE, HD	Died
4	Iyoda	[11]	2005	60	F	Hemorrhage	Hemorrhage	RPGN	Rash	1230	MPA	PSL, PE	Died
5	Ito	[12]	2006	56	M	Infarct, hemorrhage	(–)	(–)	(–)	640 U	MPA	PSL	Died
6	Tang	[13]	2009	55	M	Infarct	(–)	(–)	Rash, MNM	22	MPA	PSL, CPA	Improved
7	Ku	[14]	2009	66	F	Infarct	IP	(–)	MNM	1719 AAU	MPA	PSL	Improved
8	Isoda	[15]	2010	72	M	Infarct, hemorrhage	(–)	(+)	MNM	330	(–)	PSL, IVCY, PE, DFPP	Improved
9	Matsuda	[16]	2011	65	M	Infarct	Hemorrhage	RPGN	GI	670	MPA (brain)	PSL, PE	Died
10	Sassi	[17]	2011	48	M	Hemorrhage	(–)	(+)	MNM, myositis	Elevated	MPA	PSL, PE	Improved
11	Ozkul	[18]	2011	55	F	Medullary infarct	Consolidation	(–)	MNM, retina	87.5 RU/mL	MPA	PSL, IVCY	Improved
12	Kimura	[19]	2012	44	F	SAH	(+)	RPGN	(–)	312	MPA	PSL, IVCY, HD	Improved
13	Present case		2012	82	M	Infarct	(–)	RPGN	Rash, retroperitoneum	150	MPA (brain)	PSL	Died

SAH subarachnoid hemorrhage, IP interstitial pneumonia, RPGN rapidly progressive glomerulonephritis, GI gastrointestinal, DIC disseminated intravascular coagulation, MNM mononeuropathy multiplex, PSL prednisolone, CPA cyclophosphamide, IVCY intravenous cyclophosphamide, PE plasma exchange, CAPD continuous ambulatory peritoneal dialysis, HD hemodialysis, DFPP double filtration plasma apheresis

in other organs including kidneys (with slight glomerular abnormalities with pauci-immune deposit by immunofluorescence microscopy), brain (with small infarct), testes, iliopsoas muscle, and skin. Liver (1330 g), kidneys (lt. 130; rt. 140 g), and spleen (95 g) were anemic. Other major findings included hypertrophy and ventricular dilatation of the heart (500 g) and congestion of the lungs (lt. 510; rt. 605 g).

Further detailed histological examination was performed in the brain. As mentioned earlier, necrotizing vasculitis in the cerebral arteries was occasionally noted (Fig. 6). MPO was immunostained with polyclonal rabbit anti-human myeloperoxidase (dilution 1/10,000; Dako Cytomation, Denmark) as the primary antibody, and biotinylated goat anti-rabbit IgG (Nichirei Bioscience, Japan) was used as the secondary antibody. Nuclei were stained using hematoxylin. MPO⁺ neutrophils occasionally attached to endothelial cells, and the endothelial cells were also stained with MPO (Fig. 7).

Discussion

The present case is an aged male with MPO-ANCA-associated MPA that involved multiple organs including retroperitoneum, kidneys, brain, testes, iliopsoas muscle, and skin. Although respiratory and renal involvements are common in MPO-ANCA-associated MPA, cerebrovascular involvement is rare, accounting for up to 4 % [1–3]. To our knowledge, 12 cases of brain involvement in patients with MPO-ANCA-associated vasculitis have been reported in the English literature or Japanese literature with English abstract (Table 1) [8–19]. Cases with pachymeningitis in this entity have been excluded.

As shown in Table 1, brain involvement of MPO-ANCA-associated vasculitis occurs in patients with various ages (15–82 y.o., mean 57.9 y.o.) of both sexes (M:F 7:6). The most common manifestation is infarct ($n = 7$), followed by hemorrhage ($n = 3$), infarct and hemorrhage ($n = 2$), and subarachnoid hemorrhage ($n = 1$). It has been postulated that cerebral infarct is caused by thrombophilia of necrotizing vasculitis whereas cerebral hemorrhage is caused by rupture of necrotizing vasculitis [8].

Six out of 13 cases including the present case with brain involvement in MPO-ANCA-associated vasculitis died, indicating poorer prognosis of this entity. In most cases, histological diagnosis of MPA was made by cutaneous biopsy, while the cerebrovascular pathology has been reported in only 2 cases with autopsy findings [8, 16]. In accordance with these 2 cases, necrotizing vasculitis of small blood vessels in the brain was identified in the present case. Furthermore, infiltration of MPO⁺ neutrophils into endothelial cells was confirmed for the first time

in the cerebral vessels, in agreement with the ANCA-cytokine sequence theory [4, 5]. Therefore, we believe that the present case may shed light on better understanding of this rare but important entity of cerebrovascular involvement of MPO-ANCA-associated vasculitis.

Conflict of interest All the authors have declared no competing interests.

References

1. Nakabayashi K, Sumiishi A, Sano K, et al. Tubulointerstitial nephritis without glomerular lesions in three patients with myeloperoxidase-ANCA-associated vasculitis. *Clin Exp Nephrol*. 2009;13:605–13.
2. Ito Y, Suzuki K, Yamazaki T, Yoshizawa T, Ohkoshi N, Matsumura A. ANCA-associated vasculitis (AAV) causing bilateral cerebral infarction and subsequent intracerebral hemorrhage without renal and respiratory dysfunction. *J Neurol Sci*. 2006;240:99–101.
3. Hattori N, Mori K, Misu K, Koike H, Ichimura M, Sobue G. Mortality and morbidity in peripheral neuropathy associated Churg–Strauss syndrome and microscopic polyangiitis. *J Rheumatol*. 2002;29:1408–14.
4. Minoshima S, Arimura Y, Nakabayashi K, et al. Increased release of myeloperoxidase in vitro from neutrophils of patients with myeloperoxidase-specific anti-neutrophil cytoplasmic antibody (MPO-ANCA) related glomerulonephritis. *Nephrology*. 1997;3: 527–34.
5. Csernok E. Anti-neutrophil cytoplasmic antibodies and pathogenesis of small vessel vasculitides. *Autoimmun Rev*. 2003;2: 158–64.
6. Kawashima S, Arimura Y, Nakabayashi K, Yamada A. MPO-positive cells and extracellular MPO in the glomeruli of MPO-ANCA-associated glomerulonephritis. *Nippon Jinzo Gakkai Shi*. 2009;51:56–67 (in Japanese with English abstract).
7. Kurata A, Arimura Y, Iwasawa A, et al. Identification of MPO-positive capillaries of the pleura by immunohistochemistry in MPO-ANCA associated vasculitis. *Pathol Int*. 2010;60:626–9.
8. Sasaki A, Hirato J, Nakazato Y, Tanaka T, Takeuchi H. An autopsy case of P-ANCA-positive microscopic polyangiitis with multiple cerebral hemorrhagic infarction. *No To Shinkei*. 1998;50:56–60 (in Japanese with English abstract).
9. Deshpande PV, Gilbert R, Alton H, Milford DV. Microscopic polyarteritis with renal and cerebral involvement. *Pediatr Nephrol*. 2000;15:134–5.
10. Saito T, Tsuchiya M, Shikata C, et al. Microscopic polyangiitis associated with marked systemic bleeding tendency caused by disseminated intravascular coagulation. *Intern Med*. 2003;42: 850–5.
11. Iyoda M, Ito J, Nagai H, et al. Microscopic polyangiitis after silicone breast implantation. *Clin Exp Nephrol*. 2005;9:252–4.
12. Ito Y, Suzuki K, Yamazaki T, Yoshizawa T, Ohkoshi N, Matsumura A. ANCA-associated vasculitis (AAV) causing bilateral cerebral infarction and subsequent intracerebral hemorrhage without renal and respiratory dysfunction. *J Neurol Sci*. 2006; 240:99–101.
13. Tang CW, Wang PN, Lin KP, Huang DF, Wang SJ, Chen WT. Microscopic polyangiitis presenting with capsular warning syndrome and subsequent stroke. *J Neurol Sci*. 2009;277:174–5.
14. Ku BD, Shin HY. Multiple bilateral non-hemorrhagic cerebral infarctions associated with microscopic polyangiitis. *Clin Neurol Neurosurg*. 2009;111:904–6.

15. Isoda K, Nuri K, Shoda T, et al. Microscopic polyangiitis complicated with cerebral infarction and hemorrhage: a case report and review of literature. *Nihon Rinsho Meneki Gakkai Kaishi*. 2010;33:111–5 (in Japanese with English abstract).
16. Matsuda H, Harada T, Ando Y, et al. Case of microscopic polyangiitis accompanied by central nervous system symptoms and brain vasculitis observed histopathologically. *Nihon Jinzo Gakkai Shi*. 2011;53:648–53 (in Japanese with English abstract).
17. Sassi SB, Ghorbel IB, Mizouni H, Houman MH, Hentati F. Microscopic polyangiitis presenting with peripheral and central neurological manifestations. *Neurol Sci*. 2011;32:727–9.
18. Ozkul A, Tataroglu C, Kiylioglu N, Akyol A, Tataroglu C. Microscopic polyangiitis presenting with medullary infarct. *J Neurol Sci*. 2011;300:173–5.
19. Kimura H, Akutsu N, Shiomi R, Kohmura E. Subarachnoid hemorrhage caused by ruptured intracranial fusiform aneurysm associated with microscopic polyangiitis. *Neurol Med Chir (Tokyo)*. 2012;52:495–8.