—Short Communication—

A Case of Microscopic Polyangiitis with Subarachnoid Hemorrhage and Cardiovascular Complications

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Microscopic polyangiitis (MPA) is a primary systemic vasculitis that predominantly affects small and medium vessels. MPA is rarely complicated with central nervous system or cardiovascular disease.
We report a very rare case of MPA complicated with cerebral infarction, cardiovascular disease, and fatal subarachnoid hemorrhage in a 54-year-old man. During the first six days of hospitalization the patient was diagnosed with rapid progressive glomerulonephritis (RPGN), cerebral infarction, and unstable angina. According to patient's symptoms and laboratory findings, were consisted with a diagnosis of severe MPA. Steroid pulse therapy was immediately introduced. However, the patient developed massive subarachnoid hemorrhage on the 8th day of hospitalization. The condition progressively deteriorated, and the patient died on the 33rd hospital day. (J Nippon Med Sch 2017; 84: 251–255)

Key words: microscopic polyangiitis, cerebral infarction, unstable angina, subarachnoid hemorrhage

Introduction

MPA is a primary systemic vasculitis classified as an anti-neutrophil cytoplasmic antibody associated vasculitis (AAV) that predominantly affects small and medium vessels. MPA commonly presents with renal and lung dysfunction, but is rarely complicated with central nervous system or cardiovascular disease. We report an extremely rare case of MPA that caused cerebral infarction, unstable angina, and fatal subarachnoid hemorrhage.

Case Report

A 54-year-old man was admitted to our emergency department complaining of appetite loss and vomiting over the past month. He had also lost 3 kg of body weight. His past medical history included hypertension, for which he took antihypertensive medicine. He had no overt symptoms of renal failure and denied having bloody stool.

On examination, his level of consciousness was normal, he had no pyrexia, his blood pressure was 121/85 mmHg, heart rate and his was 82 bpm and regular.

Head, eyes, ears, nose, throat, abdominal, and skin examinations revealed no abnormalities. His cardiovascular system and neurological examinations were normal. There was no edema in either leg.

Laboratory examinations showed a white blood cell count of 8,600/μL, hemoglobin 10.8 g/dL, blood urea nitrogen 72.4 mg/dL, creatinine 6.08 mg/dL, and C-reactive protein (CRP) 12.12 mg/dL. Urinalysis showed proteinuria 3+ (79 mg/dL), creatinine 49 mg/dL, and occult blood 3+. Blood and urine cultures were negative. Abdominal ultrasonography showed a normal kidney size, without hydronephrosis. The inferior vena cava was collapsed. No abnormal findings were found in his chest computed tomography (CT). Electrocardiography was normal.

The results of the patient's initial examinations pointed to the possibility of renal failure. RPGN was suggested due to concomitant proteinuria, hematuria, and anemia, and a contributing factor to renal failure could have been his volume depletion due to vomiting and anorexia for one month. The patient was hospitalized and normal saline was administered for volume depletion, and additional laboratory tests were ordered, including anti-neutrophil cytoplasmic antibody (ANCA), anti-glomerular basement membrane-antibody, and antinuclear antibody (**Table 1**).

On the first day of hospitalization, he suddenly com-

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plained of weakness in his right leg and fell down. Neurological examination showed paralysis in the right leg with impaired sensation and motor coordination. The brain magnetic resonance imaging revealed a cerebral infarction of the anterior cerebral artery region (**Fig. 1**). We performed electrocardiography again. It showed atrial fibrillation, which had not been present at the time of hospital admission. The neurologist suspected it was a cardiogenic embolism, and started heparin. The neurologic symptoms of the patient resolved rapidly.

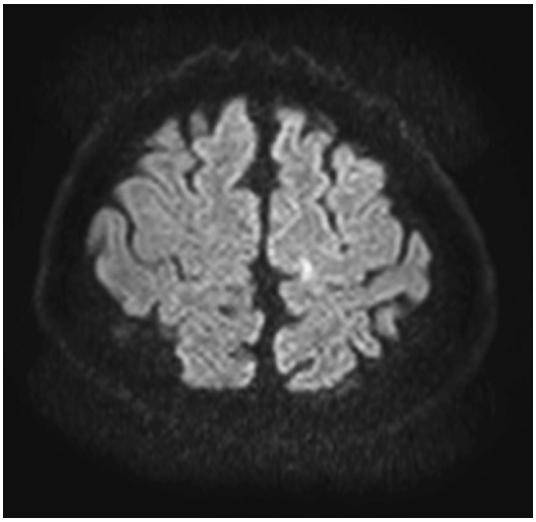

Fig. 1 Brain magnetic resonance imaging on the first hospital day. The diffusion weighted imaging (DWI) showed high-signal lesion in the anterior cerebral artery region.

On the 6th day of hospitalization he complained of chest pain.

Electrocardiography showed ST depression in leads II, III and aVF. Transthoracic echocardiography revealed mild hypokinesis. Troponin and cardiac enzyme were not elevated. The cardiologist gave a diagnosis of unstable angina. Because of severe acute kidney injury complications, coronary catheterization was postponed. Nitroglycerin and landiolol hydrochloride were administered by intravenous injection. This treatment promptly resolved both the chest discomfort and ST changes in the electrocardiogram.

During the patient's hospitalization, normal saline hydration was maintained and kidney function improved slightly. His creatinine decreased from 6.08 to 4.70 mg/dL. However, on the 8th day the laboratory blood tests revealed a strong positive value (604 U/mL) of myeloperoxidase-ANCA (MPO-ANCA). Based on the patient's symptoms and laboratory findings, he was diagnosed with severe MPA with RPGN and cerebral infarction. Steroid pulse therapy was immediately introduced with intra venous methylprednisolone, 500 mg daily, for 3 days. On the third day of steroid therapy, he suddenly became comatose due to a massive subarachnoid hemorrhage (**Fig. 2**, **Fig. 3**). Emergent brain 3D CT was performed, but no aneurysm was seen. Conventional craniotomy was performed. However, his condition progres-

Table 1 Laboratory findings on admission

Peripheral blood		Blood chemistry		Serological test		Urinalysis	
WBC	8,600 /μL	ALP	257 IU/L	CRP	12.12 mg/dL	pH	5.5
RBC	3,740,000 /μL	AST	14 IU/L	HCV	(–)	Sp.Gr	1.014
Hb	10.8 g/dL	ALT	14 IU/L	HBV	(–)	Protein	(3+)
Ht	32 %	γGTP	117 IU/L	TPHA	(–)		1.6 g/gCr
MCV	84 fL	LDH	255 IU/L	HIV	(–)	Glucose	(–)
MCH	29 pg	TP	8.6 g/dL	ANA	(–)	Occult blood	(3+)
MCHC	34 g/dL	ALB	3 g/dL	MPO-ANCA	604 IU/mL	RBC Cast	(1–4/HPF)
Plt	3,800 /μL	Cr	6.08 mg/dL	PR-3 ANCA	(–)		
		BUN	72.4 mg/dL	anti GBM-Ab	(–)		
		UA	10.7 mg/dL	CH50	60 U/mL		
Coagulation		T-Bil	0.3 mg/dL	C3	114 mg/dL		
PT-T%	87 %	HbA1C	5.9 %	C4	33 mg/dL		
APTT	13.7 sec	FBS	99 mg/dL	IgG	2,592 mg/dL		
D-dimer	3.9 mg/mL	TC	178 mg/dL	IgA	252 mg/dL		
		TG	168 mg/dL	IgM	294 mg/dL		
		Na	135 mEq/L				
		K	3.5 mEq/L				
		Cl	99 mEq/L				
		Ca	7.7 mg/dL				
		P	5.8 mg/dL				

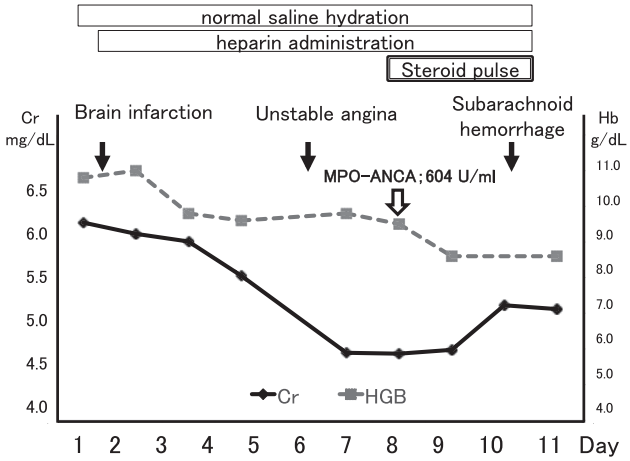

Fig. 2 Clinical course. Cr gradually decreased during normal saline hydration which made us hesitate to start immediate steroid therapy.
The black arrows indicate the onset of brain infarction, unstable angina, and subarachnoid hemorrhage, the white arrow indicates the time when MPO-ANCA was revealed.

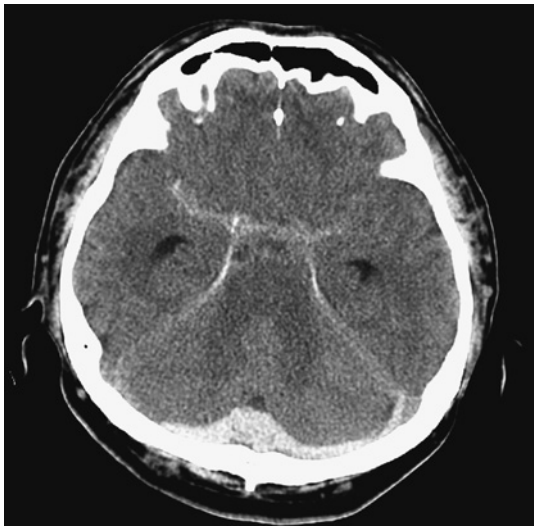

Fig. 3 Brain CT showing subarachnoid hemorrhage on the 8th hospital day. There was no aneurism.

sively deteriorated, and he died on the 33th hospital day. An autopsy was not performed.

Discussion

MPA is a systemic vasculitis characterized by inflammation of small and medium vessels and the presence of ANCA[1]. In Japan, MPA is the predominant type of AAV, accounting for 70–80% of all AAV cases. More than 90% of the MPA patients are positive for MPO-ANCA[2,3]. Although MPA is a multiple organ disease, renal involvement is the most frequent manifestation, with about 60% of MPA patients presenting with RPGN[4]. Other organ manifestations include the lung, gastrointestinal tract, skin, joints, and peripheral nervous system. First, we diagnosed our patient with RPGN according to the disease definition of the World Health Organization. It defines RPGN as an abrupt or insidious onset of macroscopic hematuria, proteinuria, anemia, and rapidly progressing renal failure, all of which were seen in this patient. MPO-ANCA was also detected in this patient. According to the diagnostic criteria of the Ministry of Health, Labor and Welfare of Japan, the concomitance of RPGN and MPO-ANCA indicated that this patient had MPA. It was classified as one of the most severe types due to the associated subarachnoid hemorrhage[5].

Cerebrovascular involvement, especially subarachnoid hemorrhage, with MPA is very rare[6,7]. Sakaguchi et al. proposed the following pathophysiology: cerebral infarction is caused by thrombophilia due to necrotizing angiitis, while cerebral hemorrhage is caused by the rupture of necrotizing angiitis[8]. The artery, made weak by MPA, ruptured and intracranial bleeding was thought to occur. However, we cannot exclude the possibility that cerebral infarction occurred due to cardiogenic embolism as the patient had atrial fibrillation. It is unlikely that heparin caused the subarachnoid hemorrhage because the heparin administered was within the established therapeutic range, his activated partial thromboplastin time was within the therapeutic range, and his blood pressure was normal. We need to be aware of rare but fatal symptoms of MPA such as intracranial hemorrhage.

Cardiac involvement with AAV is often seen in Eosinophilic granulomatosis with polyangiitis[9], but is not often associated with MPA[10]. There is a case report of eosinophilic granulomatosis with polyangitis with acute coronary syndrome caused by coronary vasospasms[11]. Our patient complained of chest pain that was resolved with nitroglycerin, which is compatible with a diagnosis of coronary vasospasms. Since the patient had no risk factors for cardiovascular diseases, except hypertension, he was less likely to develop unstable angina during the course of his MPA. The possibility of cardiac involvement with MPA was much more likely.

It is very rare that cerebral infarction and subarachnoid hemorrhage occur simultaneously[12]. To our knowledge this is the first case in which cerebral infarction, unstable angina, and fatal subarachnoid hemorrhage appeared consecutively within a very short period of time.

The therapeutic approach for MPA is based on disease severity. MPA with cerebral hemorrhage is categorized as an extremely severe form of MPA. The recommended

treatment for the most severe types of MPA is steroids, cyclophosphamide (CY) and plasma exchange (PE)[5]. Kimura et al. reported the successful clinical course of MPA complicated with subarachnoid hemorrhage with a combination therapy of steroids and CY[13], and Isoda et al. treated MPA with cerebral infarction and hemorrhage, with steroid therapy, and PE, resulting in remission[14]. However, another MPA patient with multiple cerebral hemorrhages treated with steroids and CY died[15].

The therapeutic management for MPA causing cerebrovascular diseases is very challenging. Age, lung involvement, renal function, and a high level of CRP are identified as prognostic predictors. Survival rates for MPA in Japan at 6 months, 1 year, and 2 years, are 82.6%, 79.3%, and 72.3% respectively[16], however, MPA patients complicated with cerebrovascular diseases tend to have a much worse prognosis[17]. In our case the disease was so rapid and so progressive that there was no time to induce remission by treatment with CY or PE, in addition to steroid therapy.

Our case highlights two points. First, MPA can present with rare symptoms. Second, rapid initial diagnosis of MPA presenting with uncommon symptoms, is crucial because it often takes time to get the results of a definitive blood analysis such as MPO-ANCA or the results of histological examinations. We need to recognize atypical systemic symptoms related to MPA in order to treat timely.

Conclusion

MPA is a systemic and very progressive vasculitis causing not only renal complications but also cerebral and cardiovascular diseases. We should be careful to consider the presence of rare cases, in order to provide appropriate treatment without delay.

Conflict of Interest: The authors declare no conflicts of interest.

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(Received, September 30, 2015)
(Accepted, February 9, 2016)