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CASE REPORT

Development of intracerebral hemorrhage in the short-term clinical course of a patient with microscopic polyangiitis without neurological symptoms at diagnosis: an autopsy case

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Abstract A 77-year-old man with high-grade fever, progressive renal dysfunction, high serum level of C-reactive protein and positive serum myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) was diagnosed with microscopic polyangiitis with rapidly progressive glomerulonephritis, and remission induction treatment with glucocorticoids and intravenous cyclophosphamide was initiated. Although his general condition improved in a short time, intracerebral hemorrhage occurred 12 days after the initiation of treatment and emergent hematoma evacuation was performed. However, he passed away on day 14. Surprisingly, even though no clinical findings for any organs except for renal involvement was detected before his death, autopsy revealed necrotizing vasculitis affecting various systemic organs including kidney, pancreas, liver, myocardium in ventricle, adipose tissue of the left adrenal gland, small intestine, gallbladder, bronchus, prostate, testis and spleen. It is difficult to detect widespread vasculitis without clinical symptoms and signs in patients with ANCA-associated vasculitis. A whole body assessment tool is necessary to detect unexpected vital organ damage, including cerebral vessels.

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic autoimmune disease of unknown cause that affects small to medium-sized blood vessels and is often positive for ANCA. There are geographic and ethnic differences in the relative incidence of different clinical phenotypes, such as microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA). According to a previous report, the frequency of respiratory involvement in renal vasculitis including MPA and GPA is similar between UK and Japan, whereas the frequency of neurological involvement is significantly lower in Japan [1]. Among neurologic manifestations in patients with MPA, intracerebral hemorrhage has rarely been reported, but it leads to poor outcomes [2].

We describe the case of a patient with MPA who showed no neurological symptoms at the time of diagnosis of MPA, but who later developed intracerebral hemorrhage caused by autopsy-proven cerebral vasculitis in his short-term clinical course, while general and other vasculitis symptoms were improved by the initial treatment.

Case report

A 77-year-old man with high-grade fever and loss of appetite was referred and admitted to our hospital in 2013. His fever had persisted for a month before the referral and hadn't improved by antibiotic treatment. He had previously

been treated for asthma, diabetes mellitus, and hypertension at the local hospital.

On the admission, he presented with bilateral leg edema, loss of appetite, and a weight loss of ~5 kg within a month. His body temperature was 38.5 °C and his blood pressure was 98/54 mmHg. His consciousness was clear and he had no symptoms suggestive of neurological, respiratory, or abdominal involvement. Laboratory findings are summarized in Table 1. The levels of serum creatinine (Cr, 1.67 mg/dl; 6 days prior it was 1.13 mg/dl) and C-reactive protein (CRP, 21.5 mg/dl) had increased and myeloperoxidase (MPO)-ANCA was elevated (128.0 IU/mL; normal range <3.5 IU/mL). Urinalysis showed urinary protein excretion of 0.87 g/day and sediment containing 1–4 red blood cells (RBCs) per high power field and 20 granular casts per whole field. Computed tomography (CT) showed no signs of lung involvement such as alveolar hemorrhage or interstitial lung disease. We made a clinical diagnosis of MPA manifesting rapidly progressive glomerulonephritis.

Oral prednisone (0.8 mg/kg/day) concomitant with intravenous 300 mg of cyclophosphamide was initiated as remission induction therapy. The clinical course of this patient is shown in Fig. 1. His general symptoms such as fever, loss of appetite, and general malaise improved dramatically a few days after initiation of treatment (Fig. 1). The serum level of CRP normalized and levels of serum Cr level decreased from 1.81 to 1.35 mg/dl.

Ten days after initiation of the treatment, loss of consciousness with a Glasgow Coma Scale score of 7 and loss of light reflex occurred shortly after he complained of a headache. His temperature was 36.4 °C, blood pressure was 158/80 mmHg, and heart rate was 74 beats per minute. Cranial CT scan detected an acute lesion of thalamus hemorrhage rupturing into the bilateral ventricle (Fig. 2). Although an emergent hematoma evacuation was performed, he died 2 days after the onset of the intracerebral hemorrhage.

An autopsy was performed 17 h after death. Macroscopic findings revealed bleeding from the thalamus that had ruptured into the left cerebral ventricle (Fig. 3a). Microscopic examination revealed fibrinoid necrosis and neutrophilic infiltration in the small and medium sized arteries of the thalamus, cerebellum, and brain stem with a segmental distribution and perforation to the ventricle, and no aneurysm was detected. In addition, renal arteriolitis with fibrinoid necrosis was also observed, and crescent formation was seen in approximately 2 % of the glomeruli (Fig. 3b). Surprisingly, microscopic findings revealed necrotizing vasculitis affected many organs including pancreas, liver, heart ventricle, adipose tissue of the left adrenal gland, small intestine, gallbladder, bronchus, prostate, testis, and spleen in spite of no vasculitis symptoms (Fig. 4). In this case, there were slightly crescentic formation,

Table 1 Laboratory data

Peripheral blood	
WBC (/μl)	18720
RBC ($\times 10^4$/μl)	281
Hb (g/dl)	8.7
PLT ($\times 10^4$/μl)	21.0
Blood chemistry	
AST (IU/l)	52
ALT (IU/l)	24
γGTP (IU/l)	26
ALP (IU/l)	484
LDH (IU/l)	282
CK (U/l)	53
UA (mg/dl)	4.0
TP (g/dl)	5.2
Alb (g/dl)	1.3
BUN (mg/dl)	35.0
Cr (mg/dl)	1.67
Na (mmol/l)	130
K (mmol/l)	3.9
Cl (mmol/l)	99
Ca (mg/dl)	7.4
HbA1c (%)	7.2
Serological test	
CRP (mg/dl)	21.5
PCT (U/ml)	2.1
IgG (mg/dl)	1866.5
IgA (mg/dl)	251.0
IgM (mg/dl)	62.1
IgE (IU/ml)	58
C3 (mg/dl)	54.6
C4 (mg/dl)	2.3
CH50 (U/ml)	10
PR3-ANCA (IU/ml)	<0.50
MPO-ANCA (IU/ml)	128.0
Anti-GBM-antibody (U/ml)	2.56
Urinalysis	
Proteinemia	(+)
Sediment RBC	(−)

PCT procalcitonin; *PR3-ANCA* proteinase-3-antineutrophil cytoplasmic antibody; *MPO-ANCA* myeloperoxidase-antineutrophil cytoplasmic antibody; *GBM* glomerular basement membrane

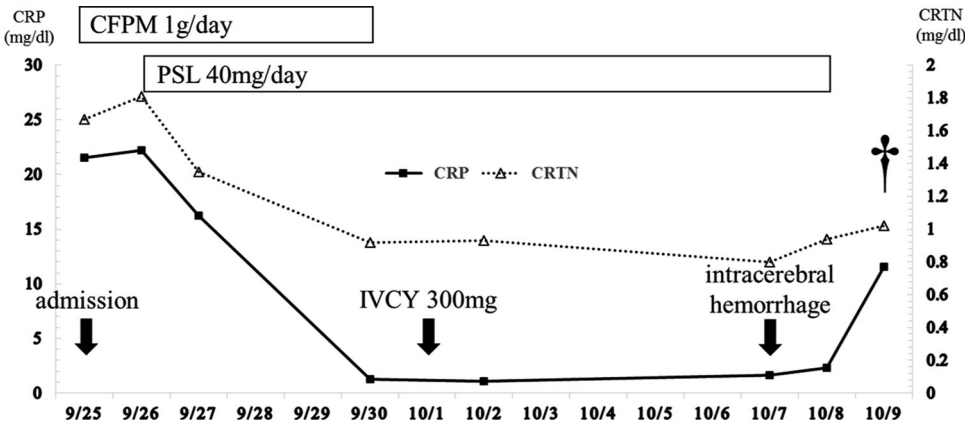

Fig. 1 Clinical course. *CFPM* cefepime; *PSL* prednisolone; *IVCY* intravenous pulse cyclophosphamide

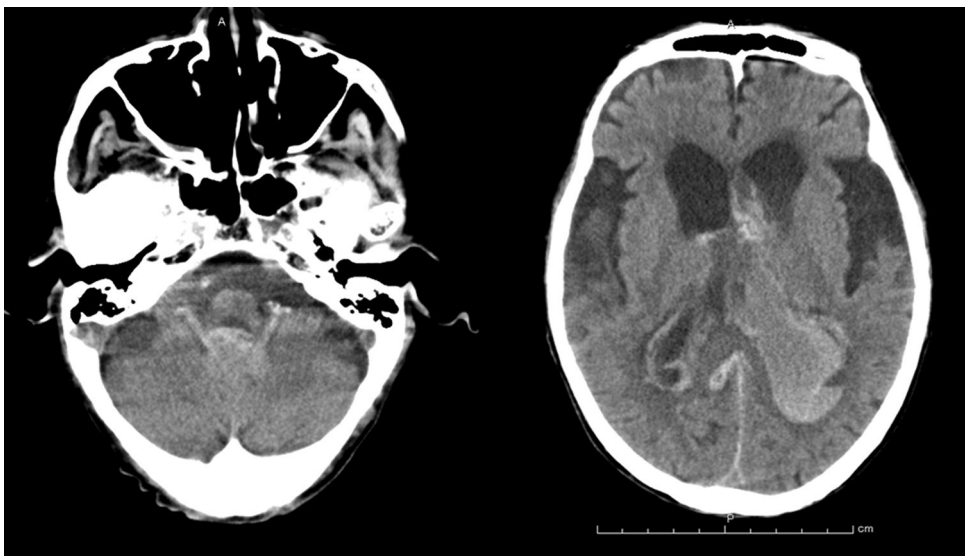

Fig. 2 Cranial CT imaging showing an acute lesion of *left-sided* intracerebral hemorrhage that ruptured into the lateral ventricle

therefore, we were finally rather diagnosed with MPA than polyarteritis nodosa.

Discussion

We experienced a case of a patient with MPA who developed intracerebral hemorrhage caused by autopsy-proven cerebral vasculitis, although his general and other vasculitis symptoms were improved by the initial treatment. Autopsy also detected widespread vasculitis in organs such as the kidney, pancreas, liver, ventricular myocardium, adipose tissue of the left adrenal gland, small intestine, gallbladder, bronchus, prostate, testis, and spleen. Even though MPA patients who developed cerebral vascular disorders without neurological finding might not be rare, it is important that widely affected organ was found from the results of the autopsy.

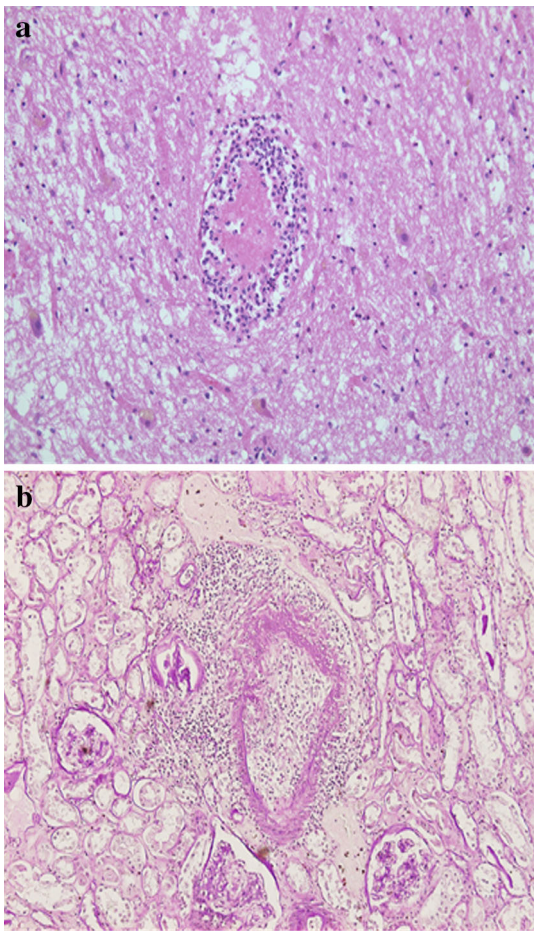

Fig. 3 **a** Autopsy revealed inflammatory involvement with fibrinoid necrosis of a small vessel in the brain. (Hematoxylin and eosin stain, original magnification ×200). **b** Crescent formation is seen in approximately 2 % of glomeruli. Angiitis of the small vessels with fibrinoid necrosis was observed, but there is no marked glomerular change in this region (hematoxylin and eosin stain, original magnification ×100)

Nine cases of cerebral hemorrhage associated with MPA were reported previously. Among these cases, vasculitis was confirmed histologically in only two cases. One case, reported by Nagasaka et al., was suspected to overlap with IgA vasculitis [3]; therefore, only one MPA patient with cerebral hemorrhage, reported by Han et al., had histological proof of pauci-immune vasculitis [4]. In that case, autopsy revealed widespread vasculitis in the brain, middle ears, larynx, trachea, adrenals, kidneys, and spleen with mucosal ulceration and micro-infarction of solid organs. It seems to be common that vasculitis is widely distributed to various asymptomatic organs. Most probably, involvement of the brain by vasculitis is related to an affected organ that was distributed broadly. We suspect that there is no relationship between the presence of cerebral vasculitis and the severity of other organ symptom. This is because in our case and in other reported cases, the severity of MPA before developing cerebral hemorrhage varied [3–11].

The European League Against Rheumatism (EULAR) recommendations for the management of vasculitis suggest selecting treatment options according to disease severity [12]. In particular, patients with vital organ failure are categorized as having severe disease and are recommended to be treated concomitantly with plasma exchange (PE). Previous reports showed that central nervous system (CNS) involvement at the time of diagnosis of vasculitis was an independent factor predictive of 1-year survival [13]. Therefore, it is important to diagnose CNS involvement as vital organ damage.

However, the present case had no clinical symptoms or signs related to vital organ involvement except for the kidney; therefore, it was extremely difficult to diagnose organ involvements other than the kidney. If there are more feasible biomarkers or imaging test which are capable of evaluation about distribution of affected organ, we may be able to prevent the cerebral vasculitic complications by additional therapy, such as PE.

In conclusion, it is difficult for present clinical practices to diagnose widespread vasculitis without clinical symptoms and signs in patients with ANCA associated vasculitis. A whole-body assessment tool may help to

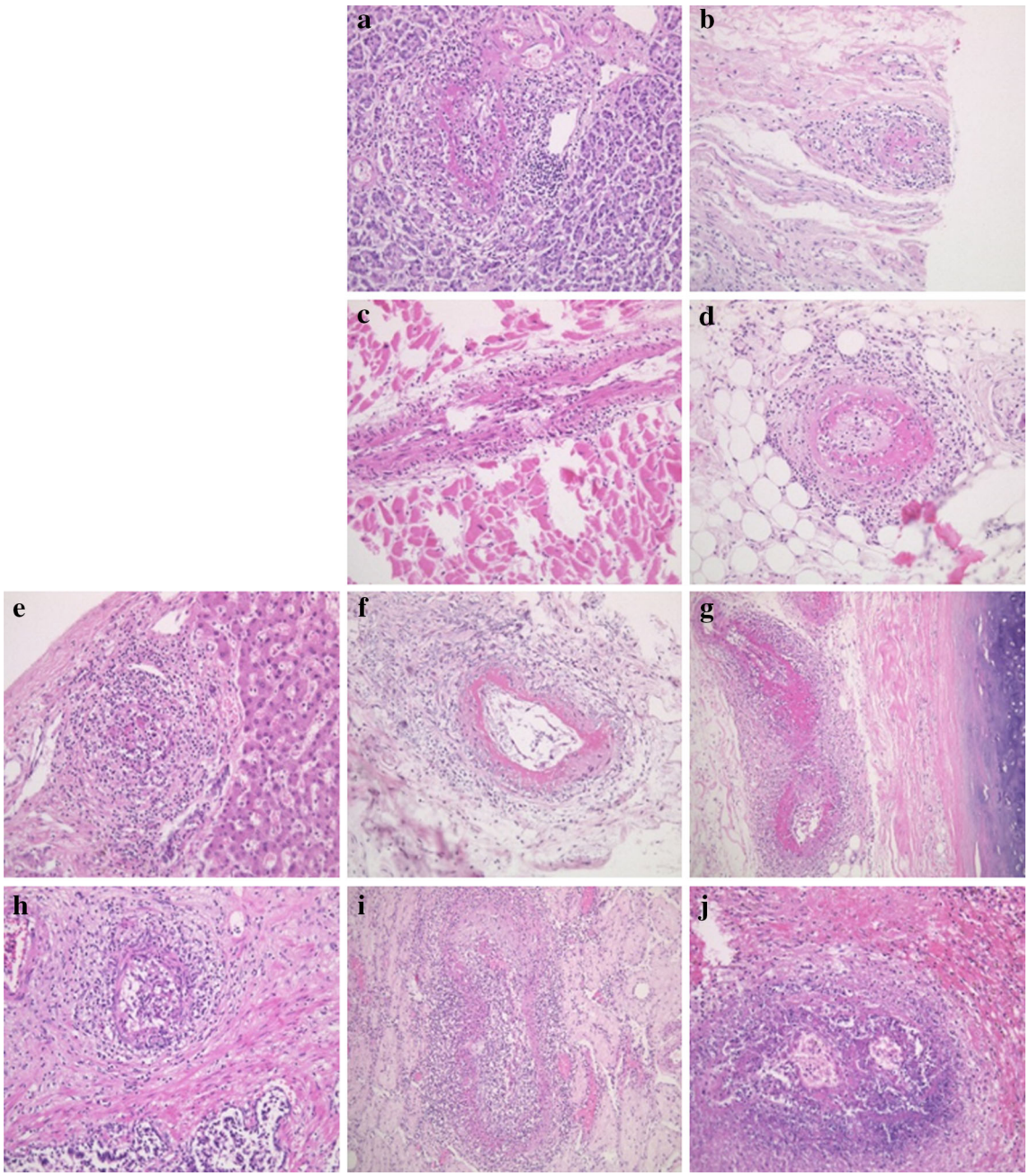

Fig. 4 Autopsy revealed necrotizing vasculitis affected in many organs including (**a**) pancreas, (**b**) liver, (**c**) ventricle in his heart, (**d**) adipose tissue of the *left* adrenal gland, (**e**) small intestine, (**f**) gallbladder, (**g**) bronchus, (**h**) prostate, (**i**) testis, and (**j**) spleen

diagnose unexpected vital organ damage and therefore affect treatment choices.

Compliance with ethical standards

Conflict of interest Jun Wada receives speaker honoraria from Astellas, Boehringer Ingelheim, Novartis, Novo Nordisk, and Tanabe Mitsubishi, and receives grant support from Bayer, Daiichi Sankyo, Kyowa Hakko Kirin, MSD, Novo Nordisk, Otsuka, Torii, Pfizer, Takeda, Taisho Toyama and Tanabe Mitsubishi.

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