Fatal hemoperitoneum due to rupture of mesenteric artery in remission state of microscopic polyangiitis, concomitant with severe hypertension and posterior reversible encephalopathy syndrome: an autopsy case report

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Abstract

Microscopic polyangiitis (MPA) is a type of necrotizing vasculitis associated with high levels of myeloperoxidase-specific antineutrophil cytoplasmic antibody (MPO-ANCA). While generally associated with renal dysfunction, MPA can also cause intraabdominal hemorrhage in rare cases. A 66-year-old man was admitted to our hospital for renal dysfunction, numbness, and weight loss for 3 months. He had no significant medical history. Renal biopsy revealed crescentic glomerulonephritis with necrotizing vasculitis, which was associated with a high serum titer of MPO-ANCA, leading to a diagnosis of MPA. Remission-induction treatment with glucocorticoids and rituximab was initiated, which improved the patient's general condition and renal failure. His blood pressure was elevated and was controlled by amlodipine treatment. Two months after discharge, he visited the emergency department because of chest pain. A diagnosis of acute cardiovascular syndrome was suggested; however, his cardiac artery was not stenotic. The patient's blood pressure was high despite antihypertensive therapy, and he developed posterior reversible encephalopathy syndrome (PRES). Despite intensive treatment, the patient died 3 days later. An autopsy revealed that the cause of death was hypovolemic shock due to massive intra-abdominal hemorrhage from the ruptured mesenteric artery involved in vasculitis. In cases of MPA with sudden-onset chest or abdominal pain, a ruptured intra-abdominal artery should be considered. Secondary hypertension associated with vasculitis should be carefully managed to prevent hemorrhagic complications and PRES.

Keywords Microscopic polyangiitis · Hemoperitoneum · Secondary hypertension · Posterior reversible encephalopathy syndrome · Autopsy

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a form of necrotizing vasculitis with few or no immune deposits that predominantly affects the small blood vessels (i.e., capillaries, venules, arterioles, and small arteries) and is associated with elevated serum levels of myeloperoxidase-specific ANCA (MPO-ANCA) or proteinase 3-specific ANCA (PR3-ANCA) [1]. Microscopic polyangiitis (MPA) is categorized as an MPO-ANCA-related AAV and is usually associated with renal dysfunction, pulmonary hemorrhage, interstitial pneumonia, and peripheral nerve dysfunction. Intraabdominal hemorrhage, or hemoperitoneum, is a rare manifestation of MPA. Hemoperitoneum progresses rapidly with a poor prognosis; however,

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its clinical diagnosis is extremely difficult. Only six cases of MPA associated with hemoperitoneum have been described in the English literature [2–7].

Herein, we describe an unusual case of MPA, in which the patient complained of recurrent chest pain of unknown cause while in remission for MPA and eventually developed treatment-resistant severe hypertension, resulting in a fatal peritoneal hemorrhage due to rupture of the inflamed mesenteric artery and posterior reversible encephalopathy syndrome (PRES). This is the first case which developed hemoperitoneum in remission state of MPA.

Case report

Clinical features and laboratory findings

A 66-year-old Japanese man was referred to his primary physician with a one-week history of general fatigue and lower extremity hyperesthesia and numbness; however, the cause of his symptoms was unclear at that time. Three months later, he was transferred to our hospital for investigation of general fatigue and numbness. The patient had no remarkable family history and was on flunitrazepam and suvorexant for insomnia, which was unrelated to his current condition. On initial presentation, his vital signs were as follows: blood pressure, 102/46 mmHg; heart rate, 82 beats per minute; respiratory rate, 18 breaths per minute; oxygen

saturation, 97%; and temperature, 36.9 °C. His body weight had decreased by 5 kg within 3 months. He did not have a cough, chest pain, abdominal pain, fever, headaches, visual loss, dry eyes, or dry mouth. Physical examination revealed numbness in the right fingers and toes and vibration loss in the lower legs. The results for the patient's blood tests, renal function tests, urine analysis, serological tests, and immunological tests are included in Table 1. CT revealed pleural plaques without evidence of pulmonary hemorrhage or interstitial pneumonia and no atrophic changes in the kidneys. A nerve conduction study identified severe motor and sensory axonal neuropathies. The renal biopsy specimen showed cellular crescentic formation in 23% (6/26) of the glomeruli (Fig. 1a). The tubulointerstitium exhibited severe interstitial infiltration of neutrophils and lymphocytes in 60% of the cortex. The proximal tubular epithelium was swollen and showed detachment of the brush borders, indicating an acute tubular injury. Fibrinoid necrotic vasculitis was observed in some interlobular arteries (Fig. 1b). Immunofluorescent studies demonstrated no staining for IgG, IgA, IgM, complement (C3, C1q), or fibrinogen. Electron microscopy also showed no electron-dense deposits. MPA was diagnosed based on rapid progressive glomerulonephritis, mononeuritis multiplex, and the histological findings of necrotizing vasculitis. Although the rheumatoid factor was detected, rheumatoid arthritis was excluded because the patient did not show joint tenderness or swelling. The patient's Birmingham vasculitis

Table 1 Test results on admission

		Biochemistry and serology		Immunological test	
CBC					
WBC	10,400/ μ l	TP	5.6 g/dl	ANA	< 40 X
Neut	76.9 %	Alb	2.2 g/dl	Rheumatoid factor	21 U/ml
Ly	11.8 %	AST	23 IU/l	Anti-GBM Ab	<0.5 U/ml
RBC	3.34×10^6 / μ l	ALT	22 IU/l	MPO-ANCA	221.0 IU/ml
Hb	10.5 g/dl	LDH	102 IU/l	PR3-ANCA	< 1 IU/ml
Plt	279×10^3 / μ l	γ GTP	61 IU/l	Anti-ds-DNA Ab	< 1.2 IU/ml
Urine		Cre	3.06 mg/dl	Anti-CCP Ab	<0.5 U/ml
prot	1 +	BUN	54 mg/dl	Anti-RNP Ab	< 2.0 U/ml
glu	(−)	eGFR	17 ml/min/1.73m	sIL-2R	3510 U/ml
O.B	2 +	Na	129 mEq/l	CH50	57
U-prot	1.2 g/day	K	4.9 mEq/l	Infection	
Sedimentation		Cl	95 mEq/l	HBsAg	(−)
RBC	> 100/HPF	CRP	26.59 mg/dl	HCV-Ab	(−)
Granular cast (+)		ESR	118 mm/h		

CBC complete blood count, WBC white blood cells, Ly lymphocytes, RBC red blood cells, Hb hemoglobin, Plt platelets, prot protein, glu glucose, O.B. occult blood, U-prot urine protein, eGFR estimated glomerular filtration ratio, ANA antinuclear antibody, GBM glomerular basement membrane, Ab antibody, MPO-ANCA myeloperoxidase–antineutrophil cytoplasmic antibody, PR3-ANCA proteinase 3-antineutrophil cytoplasmic antibody, ds-DNA double-strand DNA, CCP cyclic citrullinated peptide, RNP ribonucleoprotein, sIL-2R soluble interleukin-2 receptor, HBs hepatitis B surface, Ag antigen, HCV hepatitis C virus

Fig. 1 Microscopic findings of the renal biopsy. **a** 23% of glomeruli are involved in cellular crescent formation (black arrow). (PAS staining, $\times 100$) **b** Severe infiltration of inflammatory cells, including neutrophils and fibrinoid necrosis in the interlobular artery (black arrow) (H&E staining, $\times 100$). Scale bar = 100 μm (**a**, **b**)

Fig. 2 The clinical course of the present case

activity score (BVAS) was 28 points. The patient was treated with intravenous high-dose methylprednisolone therapy (1000 mg/day for 3 days), followed by 6.5 mg of betamethasone (1 mg/kg/day), and rituximab (630 mg/body mg/kg). He developed hypertension and steroid-induced diabetes mellitus after initiation of corticosteroid treatment and was prescribed 5 mg of amlodipine and 5 mg of trazenta. The patient was discharged on the 35th day after admission. Clinical and laboratory data are summarized in Fig. 2. Three months after the initiation of treatment, he was transferred to our emergency department with severe chest pain, and corticosteroid administration was tapered to 24 mg/day of methylprednisolone. The patient's temperature was 36.1 °C; heart rate, 80 beats per minute; blood pressure, 190/70 mmHg; respiratory rate, 20 breaths per minute, and oxygen saturation, 98% in room air. There was no evidence of heart murmurs or rubs. The patient's laboratory test results are given in Table 2. An electrocardiogram showed concave ST-segment elevations (1–2 mm) in V1 and V2. Chest radiography revealed no abnormalities, and coronary cineangiography revealed no obstruction; thus, a diagnosis of unstable angina was made. Chest pain improved after the administration of a vasodilator (isosorbide dinitrate 10 mg/day); however, the next day,

Table 2 Test results on chest pain

Biochemistry and serology			
CBC			
WBC	8200/ μl	TP	5.3 g/dl
Neut	74.3%	Alb	3.6 g/dl
Ly	18.0%	AST	19 IU/l
RBC	$5.04 \times 10^6/\mu\text{l}$	ALT	22 IU/l
Hb	15.1 g/dl	LDH	501 IU/l
Plt	$111 \times 10^3/\mu\text{l}$	γGTP	79 IU/l
Urine		Cre	1.92 mg/dl
prot	1 +	BUN	41 mg/dl
glu	(–)	eGFR	29 ml/min/1.73m
O.B	1 +	Na	141 mEq/l
Sedimentation		K	3.7 mEq/l
RBC	10/HPF	Cl	105 mEq/l
Immunology		CRP	0.15 mg/dl
MPO-ANCA	8.5 IU/ml	Troponin-T	53 pg/ml

the patient lost consciousness and developed convulsive seizures. His blood pressure was elevated to 210/100 mm Hg. Brain magnetic resonance imaging showed a high-resolution area of bilateral occipital lobes in fluid-attenuated

Fig. 3 Magnetic resonance imaging of the brain. **a** High-signal intensity resolution areas in the bilateral postural lobes detected on fluid-attenuated inversion recovery images (white arrows). **b** Diffusion-

weighted image showing a slightly high intensity (white arrows). **c** The apparent diffusion coefficient map exhibits a mild hyperintense area (white arrows)

inversion recovery images (Fig. 3a). Diffusion-weighted images showed a slightly high signal intensity (Fig. 3b). The apparent diffusion coefficient map exhibited a mild hyperintense area (Fig. 3c). His brain waves were slow. These findings indicated brain vasogenic edema; therefore, a diagnosis of PRES was made. Antihypertensive therapy of intravenous continuous nicorandil injection was initiated. On the third day, the patient complained of severe chest pain. His hemoglobin level had decreased to 7.1 g/dl. The patient suddenly developed a cardiac pulmonary arrest. Abdominal ultrasound showed echo-free space in the Morrison's pouch. Despite intensive care, the patient

passed away. The clinical data of second hospitalization is summarized in Fig. 4. An autopsy was performed to determine the cause of his chest pain and death.

The autopsy showed anemic skin without jaundice or rash. Macroscopic examination revealed 1.4 L of bloody ascites, including coagula, in the abdominal cavity (Fig. 5a). A mesenteric hematoma was found in the splenic flexure of the transverse colon (Fig. 5b–d). No bleeding points could be detected macroscopically. Bloody pleural effusion was noted in both the thoracic cavities (left, 400 mL; right, 100 mL). Both the kidneys were anemic, and weighed 139 g (left) and 120 g (right). The heart

Fig. 4 The clinical course of the second hospitalization

Fig. 4

Fig. 5 Macroscopic and microscopic autopsy findings: **a–d** macroscopic findings, **e, f** microscopic findings of the mesenteric artery. **a** Bloody ascites in the abdominal cavity. **b** The mesenteric hematoma is located in the splenic flexure of the transverse colon. **c** and **d** Mesenteric hematoma and hemorrhage were observed in the surrounding adipose tissue. **e** A ruptured peripheral branch of the mesenteric artery with transmural hemorrhage. (H&E staining, $\times 40$). **f** Intimal elastic fibers of the left side of the arterial wall are lacking (Elastica van Gieson staining, $\times 40$). Scale bar = 0.5 mm

showed mild hypertrophy of the left ventricular wall and weighed 413 g. An autopsy of the brain was not approved by his family.

Microscopically, a 2 mm-sized artery in the mesentery was ruptured with transmural hemorrhage, without fibrinoid necrosis or inflammatory infiltrate. Elastica van Gieson staining of the artery showed a torn and diminished internal elastic lamina suggesting damage due to MPA (Fig. 5f). No cystic medial necrosis, arteriosclerosis, and dissection were observed. In the renal parenchyma, 50% of the glomeruli were globally sclerotic. There was no crescent formation or active glomerular lesion in the remaining glomeruli (Fig. 6a). A severe and chronic inflammatory infiltrate was observed in the tubulointerstitium. Most of the arcuate arteries and interlobular

arteries in the bilateral kidneys exhibited severe intimal thickening and recanalization, resulting in severe stenosis of the vascular lumen (Fig. 6b). The internal and external elastic laminas of these arteries were either destroyed or fragmented (Fig. 6c), as was seen in the ruptured mesenteric artery. No amyloid deposition was detected by Congo red staining. These findings were considered scarring changes that occurred in the chronic phase of necrotizing vasculitis. Hyaline sclerosis was detected in only 5% of the renal arterioles. The myocardium showed no significant ischemic changes. The cause of death was considered hemorrhagic shock due to intra-abdominal hemorrhage. The possible causal relationship between clinical and pathological alterations and death is shown in Fig. 7.

Fig. 6 Renal histology of autopsy. **a** 50% of the glomeruli show global sclerosis. The remaining glomeruli do not show crescent formation. The interstitium shows severe chronic inflammatory infiltrate. (PAS staining, $\times 40$). **b** The arcuate artery shows marked intimal thickening and recanalization. The lumen is extremely narrow (black arrowhead) (H&E staining, $\times 100$) **c** The elastic fibers of the left side of the arterial wall are ruptured with fragmentation (black arrowhead) on Elastic van Gieson staining (H&E staining, $\times 100$). Scale bar = 100 μm

Discussion

In this study, we present the case of a patient with MPA who developed hemoperitoneum caused by rupture of the mesenteric artery. Hemoperitoneum is a rare complication

of MPO-ANCA-associated vasculitis and has been reported sporadically. The seven described cases, including our case, are summarized in Table 3 [2–7]. The male-to-female ratio was 4:3, and the age range was 66–81 years. Serum MPO-ANCA was detected in all cases. Bleeding sources were varied, such as the mesenteric, left gastric, gastroduodenal, and ileocolic arteries. The pathological findings of the four lesions revealed vasculitides with fibrinoid necrosis. Others include segmental necrosis [6] and rupture of pseudoaneurysm [7]. The clinical symptoms of two cases were abdominal pain and/or peritoneal irritation [3, 5], whereas those of the three other cases were hypovolemic shock and sudden death [2, 4, 6, 7], suggesting that the onset of the disease was sudden and progressive. In our case, the patient complained of recurrent chest pain, which is commonly caused by acute coronary syndrome [8]. Non-cardiac chest pain was frequently caused by gastroesophageal regurgitation and esophageal dysmotility [9], and no cases of hemoperitoneum associated with chest pain have been reported. Therefore, in the present case, it was difficult to make a clinical diagnosis even after clinical and imaging studies. The prognosis of hemoperitoneum is extremely poor, and six of the seven reported cases died. Interestingly, except in our case, hemoperitoneum in the reported cases occurred during the active phase of MPA [2–7]. In our case, the patient developed hemoperitoneum when MPA was in remission and no active vasculitis was found during the autopsy. The rupture of the mesenteric artery may have been due to the damage of elastic fibers in the vascular wall along with severe hypertension. Treatment-resistant severe hypertension led to PRES and the rupture of the mesenteric artery. Systemic vasculitis has recently been identified as an important cause of secondary malignant hypertension, which is a life-threatening manifestation of hypertension [10]. The pathophysiology of hypertension by small-vessel vasculitis is as follows: (1) activation of the renin–angiotensin–aldosterone system due to renal artery stenosis, (2) reduction in glomerular filtration area caused by ischemic damage of small arterioles, and (3) vascular endothelial cell damage [10]. In addition, Sada et al. reported that 19% of elderly patients with AAV who were treated with high-dose glucocorticoids developed hypertension, which was the most frequent complication in this type of vasculitis, compared to patients treated with medium-dose glucocorticoids [11]. In our case, severe peripheral renal artery stenosis and ischemic damage of the renal parenchyma were detected during the autopsy. Activation of the renin–angiotensin–aldosterone system and reduced glomerular filtration rate may have

Fig. 7 The pathophysiology for the development of hypertension and hemoperitoneum in the present case

accelerated hypertension, in addition to high-dose corticosteroid therapy, which may have made the hypertensive state more severe. In addition, despite the patient being hypertensive, only 5% of arterioles exhibited hyaline sclerosis, which is a finding of chronic hypertension, suggesting that hypertension may not have continued for a long time and developed after the onset of MPA.

PRES is a syndrome that manifests as headaches, confusion or decreased level of consciousness, visual changes, and seizures, in conjunction with the typical neuroimaging features of posterior cerebral white matter changes, which are usually reversible [12]. Only three cases of PRES associated with MPA have been reported in previous studies [13–15]. One case was associated with uremic encephalopathy [14], and the others were associated with damage to the endothelium [13, 15]. In our case, endothelial injury due to severe hypertension may have led to the development of PRES, although vascular changes in the brain could not be examined pathologically.

In this case, the renal function rapidly deteriorated, even though only 23% of the glomeruli underwent crescent formation. Thus, acute tubular injury and severe tubulointerstitial inflammation may have affected renal function. These findings also indicate ischemic changes in the renal parenchyma due to necrotizing vasculitis of the arcuate arteries, which were not included in the limited renal biopsy specimen. In an MPA case with worsening renal function and a lower number of glomerular crescents than expected, precautions must be taken against severe hypertension. In summary, we describe the first comprehensive autopsy of fatal hemoperitoneum due to rupture of the mesenteric artery in a remission state of MPA. In patients who developed MPA presenting with chest or abdominal pain of unknown cause, rupture of an abdominal artery must be included in the differential diagnosis. MPA often causes secondary hypertension, and careful control of blood pressure is pivotal, even in a remission state of MPA, to prevent vascular complications of damaged vessels.

Table 3 Characteristics of hemoperitoneum due to microscopic polyangiitis

Case	Age/sex	Primary disease	Autoanti-body	Bleeding source	Pathology	Symptom	Treatment before hemoperitoneum	Disease activity	Other organs	Associated condition	Outcome	Reference
1	78/F	Microscopic polyangiitis	MPO-ANCA	Mesentery	Granulomatous vasculitis with multinucleated giant cells, fibrinoid necrosis with neutrophilic infiltration	Anemia, sudden death	Corticosteroid pulse	Active 1 post-treatment	Liver, spleen, kidneys, GI tract, gallbladder, pancreas, ovaries, uterus	None	Died (autopsy)	2
2	69/M	Microscopic polyangiitis	MPO-ANCA	Gastroduodenal artery, splenic artery	Transmural arteritis with intramural hemorrhage	Severe intraabdominal hemorrhage	Corticosteroid, cyclophosphamide	Active	RPGN	Died due to sepsis	Died	3
3	81/M	Microscopic polyangiitis	MPO-ANCA	Small intestine and ileocecum	Vasculitis with fibrinoid degeneration	Peritoneal irritation, hypovolemic shock	Corticosteroid pulse	Active (relapse)	Hypertrophic pachymeningitis, RPGN	None	Died (autopsy)	4
4	70/F	Microscopic polyangiitis	MPO-ANCA	Left gastric artery (medium-sized)	Vasculitis	Anemia	Corticosteroid pulse	Active	RPGN, vasculitis of interlobular artery	None	Died (autopsy)	5
5	74/F	Microscopic polyangiitis	MPO-ANCA	Ileocolic artery	Segmental necrosis and intramural hemorrhage	Abdominal pain	Corticosteroid pulse	Active	RPGN	Metastatic malignant melanoma	Survival	6
6	74/M	Microscopic polyangiitis	MPO-ANCA	A branch of left gastric artery (medium-sized)	Rupture of pseudoaneurysm	Cardiopulmonary arrest	Corticosteroid pulse	Active	RPGN	None	Died (autopsy)	7

Table 3 (continued)

Case	Age/sex	Primary disease	Autoanti-body	Bleeding source	Pathology	Symptom	Treatment before hemoperitoneum	Disease activity	Other organs	Associated condition	Outcome	Reference
7	66/M	Microscopic polyangiitis	MPO-ANCA	Mesenteric artery (small)	Rupture of intimal elastic lamina	Chest pain	Prednisolone	Remission	RPGN	None	Died (autopsy)	Present case

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Availability of data and materials The dataset supporting the findings and conclusions of this case report is included in this article.

Declarations

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval All of the treatment and the examination followed the guideline laid down in the Declaration of Helsinki.

Informed consent Informed consent was obtained from the patient's family in the study.

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