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【 CASE REPORT 】

Segmental Arterial Mediolysis with Preceding Symptoms Resembling Viral Infection Hampers the Differentiation from Polyarteritis Nodosa

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Abstract:
A middle-aged man presented with a fever, arthralgia, gastrointestinal symptoms, headache, and rash. After two weeks, the patient suddenly complained of severe abdominal pain, and computed tomography revealed aneurysms in the hepatic and splenic arteries, which increased in size progressively. Given the elevated levels of inflammatory markers and orchitis, polyarteritis nodosa (PN) was initially suspected. Catheter embolization for the ruptured hepatic aneurysm and splenectomy for the large splenic ones were performed, and the pathological finding was consistent with segmental arterial mediolysis (SAM). Changes in inflammatory marker levels and aneurysmal size are also informative to differentiate SAM from PN.

Key words: segmental arterial mediolysis, polyarteritis nodosa, mild encephalitis/encephalopathy with a reversible splenial lesion, myocarditis, orchitis

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Introduction

Segmental arterial mediolysis (SAM) is a non-inflammatory arterial disorder typically involving medium-sized abdominal arteries (1). Though the etiology of SAM is not fully clarified, arterial vasospasm induced by excessive catecholamine release is thought to be the underlying mechanism (2). The associated growth of aneurysms, dissection, and rupture can occasionally be fatal, so catheter embolization or resection of the injured arteries is performed.

However, the angiographic features of SAM mimic those of polyarteritis nodosa (PN), which makes it difficult to differentiate these two disorders (3). In cases of SAM complicated with any infection, the inflammatory markers can be elevated, which can hamper an accurate diagnosis. Ultimately, a histopathological examination is required to confirm the diagnosis.

Case Report

A 50-year-old man had a fever associated with headache, watery diarrhea, arthralgia, and erythema. He consulted a local doctor and was prescribed antibiotics. After three days, his clinical condition did not improve, so he visited the emergency room in our hospital.

The patient had no remarkable medical history, drug allergy, or family history. His blood pressure was 152/110 mmHg, heart rate 92 per minute, body temperature 40.3℃, and percutaneous arterial oxygen saturation 94%. A physical examination revealed no abnormalities of the heart or lungs but showed mild tenderness in the upper abdomen, bilateral conjunctival congestion, and coin-sized non-itching erythema predominantly in the extremities. No superficial lymphadenopathies, oral or genital ulcers, or motor or sensory neuropathy was noted. The patient had dental caries on the upper left with marginal periodontitis.

The results of a blood examination on admission are shown in Table. The calculated plasma osmotic pressure de-

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Table. The Examination Data on Admission.

Urinalysis			
density	1.033	Aspartase aminotransferase	33 U/L
protein	(2+)	Alanine aminotransferase	20 U/L
sugar	(-)	Lactate dehydrogenase	322 U/L
ketone bodies	(2+)	γ-Glutamyltranspeptidase	17 U/L
occult blood	(2+)	Blood urea nitrogen	17.7 mg/dL
		Creatinine	1.03 mg/dL
Blood cell count		Amylase	123 U/L
White blood cell	11,680 /μL	Creatine phosphokinase	1,075 U/L
Stab cell	13.0 %	Myoglobin	468 ng/mL
Segmented cell	84.5 %	Troponin I	3,144 pg/mL
Monocyte	0.5 %	Sodium	129.3 mmol/L
Lymphocyte	2.0 %	Potassium	3.1 mmol/L
Red blood cell	489 $\times 10^4$/μL	Chloride	93.8 mmol/L
Hemoglobin	13.7 g/dL		
Hematocrit	38.6 %	Serology	
Platelet	7.2 $\times 10^4$/μL	C-reactive protein	21.34 mg/dL
PT-INR	1.30	Immunoglobulin G	1,267 mg/dL
APTT	36.8 s	Immunoglobulin A	195 mg/dL
Fibrinogen	640 mg/dL	Immunoglobulin M	58 mg/dL
FDP	8.8 μg/dL	TPLA	(-)
		ASO	58 IU/mL
Biochemistry		ASK	160
Total protein	6.3 g/dL	ANA	<40
Albumin	3.2 g/dL	RF	<3 IU/mL
Total bilirubin	0.8 mg/dL	PR3-ANCA	(-)
Alkaline phosphatase	132 U/L	MPO-ANCA	(-)

PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrinogen/fibrin degradation products, TPLA: treponema pallidum latex agglutination, ASO: anti-streptolysin O, ASK: anti-streptokinase, ANA: anti-nuclear antibody, RF: rheumatoid factor, PR3-ANCA: proteinase-3 anti-neutrophil cytoplasmic antibody, MPO-ANCA: myeloperoxidase anti-neutrophil cytoplasmic antibody

creased to 271.6 mosmol. Tests for influenza virus A and B antigens were negative. The serum immunoglobulin (Ig) G and M titers of herpes simplex virus examined by an enzyme immunoassay showed a non-infected pattern, while those of cytomegalovirus, rubella virus, and measles virus showed infected patterns. Serum IgG and M against Epstein-Barr virus capsid antigen and early nuclear antigen tests showed a previously infected pattern.

Transient thrombocytopenia appeared on follow-up blood examinations, and atypical lymphocytes appeared from the 2 nd to 13th hospital day. Serum polymerase chain reaction evaluations for Japanese spotted fever and tsutsugamushi disease were negative. His elevated serum creatinine kinase and troponin I levels decreased to the respective normal ranges after several days. A cerebrospinal fluid examination showed a mildly elevated protein concentration of 58 mg/dL. Blood culture demonstrated no bacterial growth, and echocardiography detected no abnormal ventricular wall motion. No vegetation on cardiac valves was noted on transesophageal echocardiography. Plain chest radiography revealed no abnormalities in his lung field. The pathological assessment of the erythema showed perivascular lymphocyte infiltration in the superficial dermis and liquefaction degeneration in the epidermis, findings that were compatible with erythema multiforme.

We initially suspected potential endocarditis or rickettsiosis, and antibiotics were introduced. On the 5th hospital day, he experienced testicular pain without parotitic symptoms and was diagnosed to have orchitis by a urologist in our hospital. He had a history of mumps in childhood, and his serum titer of IgM was not elevated. On the 10th hospital day, he suffered from sudden epigastralgia and back pain, and computed tomography (CT) showed dilatation of the hepatic and splenic arteries (Fig. 1A). Follow-up CT on the 12 th hospital day showed multiple aneurysms in a string-of-beads pattern in the hepatic artery with progressive swelling (Fig. 1B). On the 13th hospital day, severe chest and abdominal pain recurred, and CT showed hematoma spreading around the liver and extravasation (Fig. 2A). An arterial blood gas test revealed a pH of 7.618, carbon dioxide partial pressure of 18.7 mmHg, oxygen partial pressure of 114.0 mmHg, and bicarbonate level of 19.3 mmol/L, which indicated respiratory alkalosis due to hyperventilation. Angiography of the hepatic artery showed multiple aneurysms (Fig. 2B), and catheter embolization of the ruptured artery was performed.

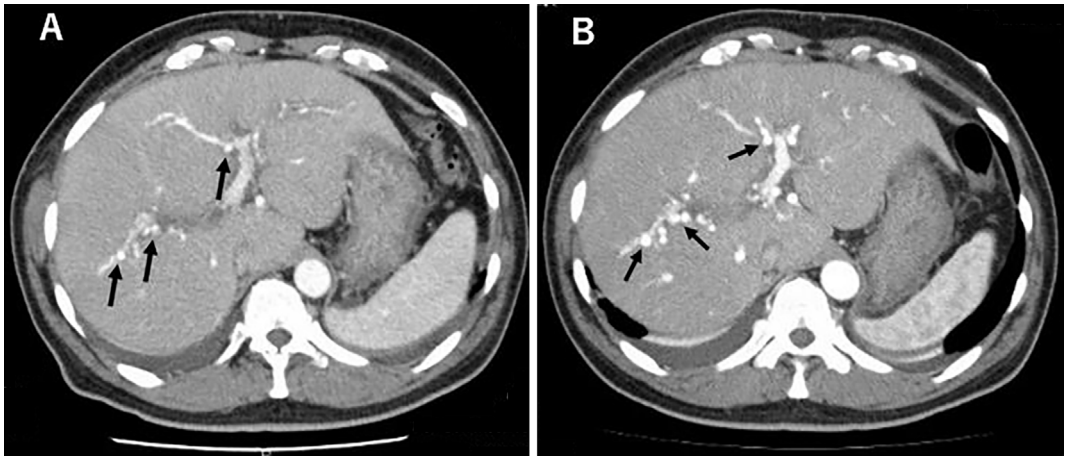

Figure 1. **CT on the 10th hospital day showed dilatation of the hepatic artery (arrow) (A), and multiple aneurysms in a string-of-beads pattern in the hepatic artery with progressive swelling were observed on the 12th hospital day (B).**

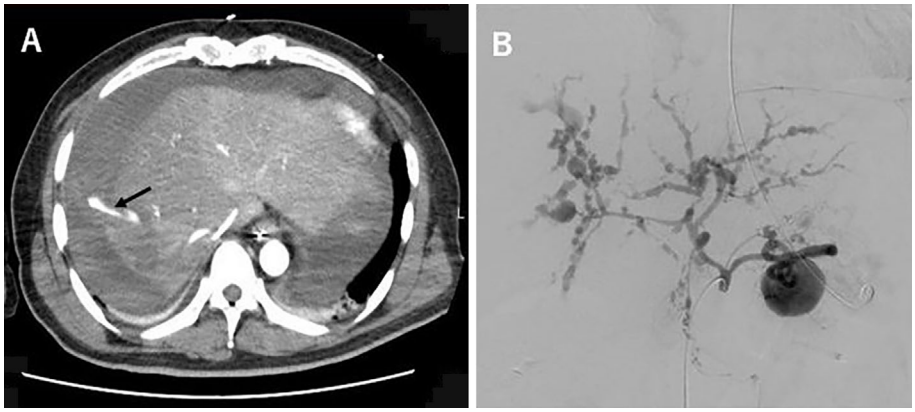

Figure 2. **On the 13th hospital day, CT showed hematoma spreading around the liver and extravasation (arrow) (A). Angiography of the celiac artery showed multiple aneurysms (B).**

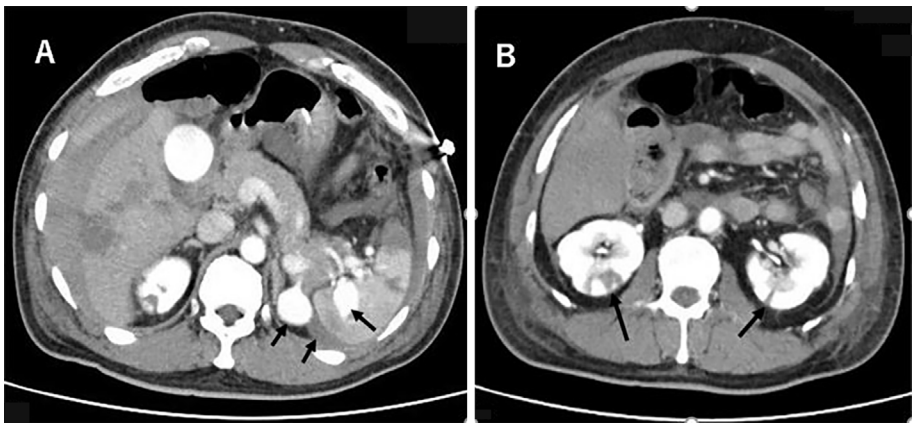

Figure 3. **CT on the 14th hospital day showed aneurysms at the splenic hilum and parenchyma as well as fluid retention around the spleen (arrow) (A) and wedge-shaped poor-contrast-enhancement regions in both kidneys (arrow) (B).**

According to the diagnostic criteria for PN revised in 2006, the diagnosis was probable PN. Given his inflammatory symptoms and examination results, we could not rule out PN without obtaining histopathological findings, and steroid therapy was started on the 13th hospital day. The following day, the aneurysms observed in the splenic hilum and parenchyma had increased in size, accompanied by fluid retention around the spleen (Fig. 3A), and wedge-shaped

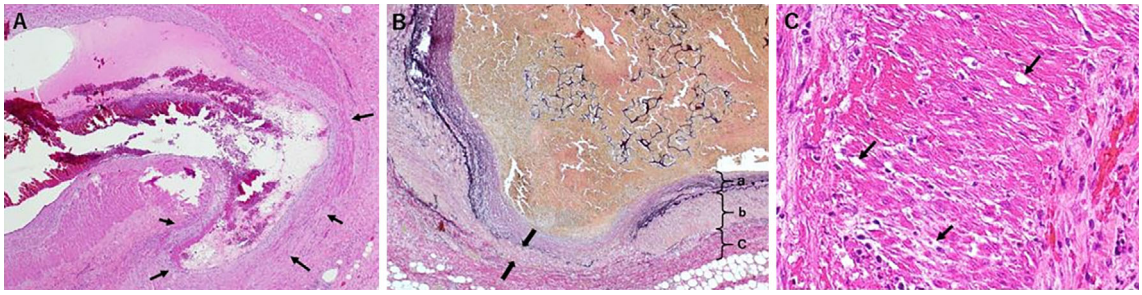

Figure 4. **Pathological findings of the splenic aneurysms consisted of segmental aneurysmal formation (arrow) [A: Hematoxylin and Eosin (H&E) staining, ×100], mediolysis and destruction of the internal and external elastic laminae (arrow) (B: Van Gieson staining, ×200), and vacuolar degeneration in media (arrow) (C: H&E staining, ×1000). a: intima, b: media, c: adventitia.**

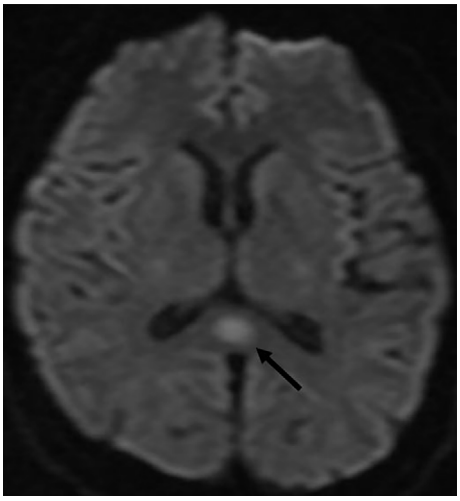

Figure 5. **Cranial MRI showed a lesion in the splenium of corpus callosum with high intensity on diffusion-weighted imaging (arrow). The lesion had spontaneously resolved after three weeks.**

poor contrast enhancement could be seen in both kidneys, indicating renal infarction (Fig. 3B). Considering the risk of rupture of the splenic aneurysm, splenectomy was performed.

The pathological findings of the large splenic aneurysm indicated mediolysis and vacuolar degeneration in the media with segmental aneurysmal formation (Fig. 4). The transarterial inflammation and fibrinoid necrosis typically seen in immune-mediated vasculitis were absent. These findings suggested SAM, so we discontinued PSL (prednisolone) on the 23rd hospital day. Cranial magnetic resonance imaging (MRI) showed a lesion in the splenium of the corpus callosum with T2 and diffusion weighted high intensity (Fig. 5), and it demonstrated a low apparent diffusion coefficient (ADC) value, which was consistent with the finding of mild encephalitis/encephalopathy with a reversible splenial lesion (MERS). On follow-up MRI three weeks later, the lesion had spontaneously resolved.

Once PSL had been stopped and the patient had recovered from his surgery, no inflammatory symptoms recurred. At seven months after splenectomy, the size of the hepatic aneurysms was stable with no progression noted on CT. The clinical course after admission is shown in Fig. 6.

Discussion

SAM is a non-atherosclerotic vascular disorder of unknown etiology usually affecting middle-aged and elderly patients (4). The initial clinical presentation is acute with abdominal or flank pain, and inflammatory markers are generally negative (5). Arterial involvement is mainly abdominal, most commonly in the splenic artery (1) but also in the renal, hepatic, and superior mesenteric arteries. The most frequent radiographical manifestation on angiography is arterial dilatation, single or multiple aneurysms giving an appearance of string-of-beads, dissecting hematomas, and stenosis and occlusion of the involved arteries (6). Treatment includes embolization, bypass, and resection of injured arteries. In addition, anti-hypertensive therapy can prevent further worsening of arterial lesions (7).

On admission, the high serum C-reactive protein (CRP) level accompanied by arthralgia and erythema multiforme in the present patient suggested the possibility of rickettsiosis or infectious endocarditis due to odontogenic infection. However, those were excluded based on the clinical data and course. The presence of aneurysms of the hepatic and splenic arteries on CT angiography coincided with the radiographic manifestations of PN and SAM. The possibility of other arterial lesions, such as fibromuscular dysplasia, mycotic aneurysm, and heritable disorders of connective tissue, was unlikely given the patient's age, gender, involved arteries, family history, and clinical course. Angiographic findings of SAM mimic those of PN, and it is sometimes difficult to differentiate these two disorders (3). The daily abdominal aneurysmal progression was too quick for the typical clinical course of PN, and there were no preceding symptoms until a few days before admission, which were also atypical features of PN. Aside from angiographic findings, the presence of orchitis, which is a characteristic feature of PN, made disease interpretation even more difficult. The final diagnosis was based on the pathological findings

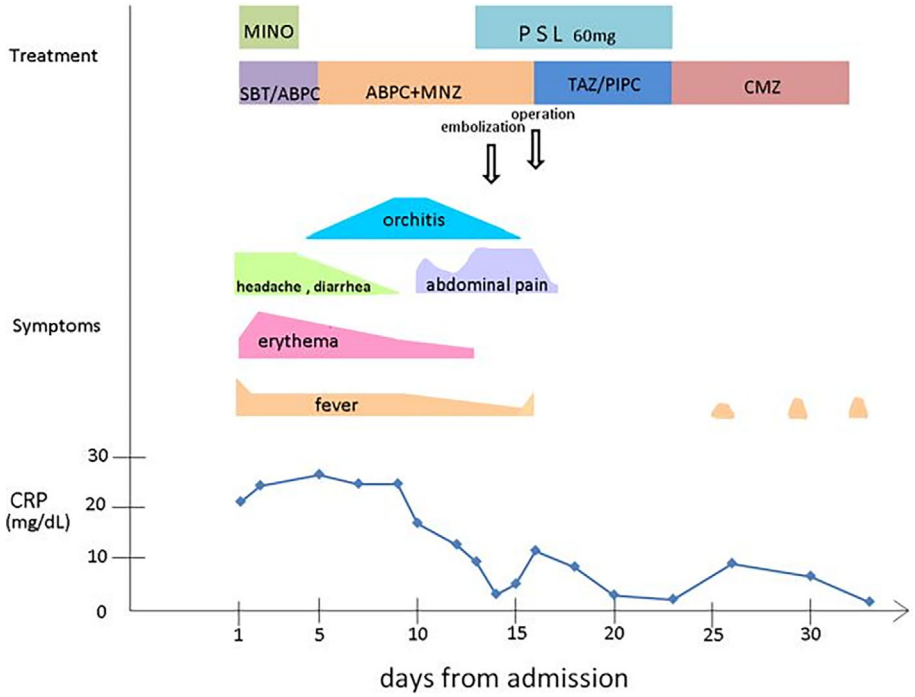

Figure 6. **Clinical course after admission. The patient's persistent high fever and serum CRP level gradually decreased from the 10th hospital day, and his abdominal pain improved after surgery. Antibiotics were continued for pancreatic postoperative fistula. CRP: C-reactive protein, MINO: minocycline, MNZ: metronidazole, PSL: prednisolone, SBT/ABPC: sulbactam/ampicillin, TAZ/PIPC: tazobactam/piperacillin, CMZ: cefmetazole**

of the arterial lesions of the surgical specimens (7).

Pathologically, SAM results from vacuolar degeneration of arterial smooth muscle, leading to mediolysis and hemorrhaging at the adventitia-medial junction and within the media. Transmural mediolysis leads to the formation of arterial wall gaps in medial dissection, and then aneurysmal and stenotic formation occurs (8, 9).

Vasospasm is thought to be the underlying etiology of SAM. Accidental catecholamine release from the peripheral nervous system in response to stress might act as a vasoconstrictor (2). Arterial lesions also develop as a result of an abnormal response of endothelial vasospasm (3). Endothelin-1 potentiates the activity of catecholamine and other pressor agents, and immunostaining reportedly showed endothelin-1 on the adventitial capillaries and neighboring arteries in SAM (10, 11). As a trigger of SAM, central nervous system lesions can initiate dysfunction of the endothelial endocrine system, causing intense vasoconstriction (12). Several arguments suggest that SAM is associated with acute psychological stress due to adrenergic hyper-reactivity through the central nervous system (13). The endothelial function and vascular response to psychological stress are damaged in patients with apical ballooning syndrome, which also causes excessive catecholamine release (14). Our patient had an attack of severe inflammation with the same symptoms caused by viral infection, which must have been a source of both mental and physical stress.

MERS is a recently proposed central nervous system disorder. The major trigger for adult-onset MERS is viral or bacterial infection, with the most common clinical symptoms being a fever, headache, and consciousness disturbance (15). The typical MRI features are transient high intensity on T2- and diffusion-weighted imaging and low ADC values. Lumbar puncture usually shows mild cytosis or normal results (16, 17). There are several hypotheses concerning the pathogenesis of MERS, including intra-myelinic edema, axonal damage, and oxidative stress (16). Most patients have mild serum hyponatremia, which might cause MERS due to osmotic demyelination (16). Complete resolution of MRI findings and clinical symptoms are hallmarks of this disorder, and the same findings were noted on a later cranial MRI examination in the present case.

Before the onset of severe abdominal pain on the 10th hospital day, our patient presented with many clinical symptoms, such as a fever, arthralgia, erythema, watery diarrhea, and testicular pain. The transient thrombocytopenia, atypical lymphocytes, and elevated myocardial markers in the peripheral blood suggested viral infection, which is also a major cause of MERS. Gastrointestinal symptoms complicated with orchitis and myocarditis are the clinical features of enterovirus infection (18-20). Although we did not measure the serum antibody titers, enterovirus infection might have been the causative pathogen. We suspect the following mechanism for SAM in the present case: viral infection caused several systemic symptoms associated with physical and mental stress, which induced hyper-secretion of catecholamine, leading to arterial vasospasm and the onset of SAM.

SAM usually shows no disease progression on follow-up

studies over several years (21), and the enhanced CT findings in our case were stable at seven months after splenectomy. When we encounter progressive abdominal aneurysm, we should be alert for the possibility of SAM and confirm the preceding symptoms, which might be related to the onset of SAM and facilitate its differentiation from other similar disorders.

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

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