

Medial medullary infarction caused by antineutrophil cytoplasmic antibody-related vasculitis

Case report and review of the literature

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Abstract

Rationale: Medial medullary infarction accounts for less than 1% of brain infarctions, and medial medullary infarctions is very rarely caused by antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

Patient concerns: We report the case of a 76-year-old man at low risk of arteriosclerosis who presented with disorders on the left side including gaze-evoked nystagmus, paralysis of the extremities, pyramidal signs, sensory disturbance, and dysesthesia. Brain magnetic resonance imaging also showed right medial medullary infarction.

Diagnoses: Medial medullary infarction caused by ANCA-related vasculitis was diagnosed based on mild renal dysfunction and high levels of blood leukocytes, C-reactive protein (CRP), and myeloperoxidase (MPO)-ANCA.

Interventions and outcomes: He underwent two 3-day courses of steroid pulse therapy involving daily 1000mg doses of methylpredonine. He then received 30 mg/day (0.5 mg/kg/day) of prednisolone (PSL) without other immunosuppressants. Levels of MPO-ANCA and the inflammatory marker CRP decreased rapidly a month after admission. Once MPO-ANCA became undetectable, the PSL dose was carefully reduced to 10mg/day. To treat his paralysis, we provided rehabilitation with a Hybrid Assistive Limb five times starting at a month post-onset. His Barthel index score rose from 45 to 70 points.

Lessons: Medullary infarction is mostly caused by arteriosclerosis and vertebral arterial dissection. When systemic inflammatory findings are obtained, ANCA-associated vasculitis should be considered a potential cause, and steroid pulse therapy should be promptly administered.

Abbreviations: ANCA = antineutrophil cytoplasmic antibody, CRP = C-reactive protein, CT = computed tomography, MPO = myeloperoxidase, MRI = magnetic resonance imaging, PSL = prednisolone, s-IL2R = interleukin-2 receptor.

Keywords: ANCA-related vasculitis, hybrid assistive limb, medial medullary infarction, MPO-ANCA

1. Introduction

Medial medullary infarction accounts for <1% of brain infarctions^[1] and is usually caused by atherothrombotic brain infarction. Other causes include large-vessel infarction (50% of

brain infarctions), artery dissection (15%), small-vessel infarction (13%), cardiac thrombosis (5%), and Moyamoya disease (<1%).^[2] In rare cases of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, the initial symptoms are those of cerebral infarction, which is difficult to distinguish from atherothrombotic cerebral infarction, leading to possible treatment delays. We report a case of medial medullary infarction caused by ANCA-associated vasculitis that was effectively treated with steroid pulse therapy.

2. Case report

A 76-year-old man noticed bilateral edema in his lower legs and livedo reticularis and a weight gain of 4 kg 1 month before being transferred to our hospital. Eleven days before the transfer, he suddenly felt dizzy at work and became unable to walk. Because weakness in the left extremities and dysarthria occurred simultaneously, he visited a nearby hospital and was diagnosed with a brainstem infarction using brain magnetic resonance imaging (MRI). Because hypertension was noticed in a medical appointment earlier in the year, he had been receiving oral amlodipine (2.5 mg/day), and his blood pressure was favorably controlled. Although he received antiplatelet therapy (intravenous infusion of ozagrel [160 mg/day], aspirin [100 mg/day], and cilostazol [100 mg/day]), left limb paralysis and dysarthria progressed. In addition, his renal function deteriorated (creati-

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nine [Cre]: 1.3 mg/dL), and a myeloperoxidase (MPO)-ANCA test result was highly positive. Because cerebral infarction associated with the vasculitis was suspected, he was therefore transferred to our hospital,

In a physical examination on admission, he was alert, had mild hypertension (146/84 mmHg), and had a regular pulse (81 beats/min). In a neurologic examination, he exhibited gaze-evoked nystagmus when looking to the left. He had dysarthria, dysphagia, and an impaired gag reflex. He had bilateral Babinski and Chaddock signs during extension, dysesthesia, and left-side extremity disorders including paresis, enhanced tendon reflexes, and impaired positional and tactile senses. He could sit upright but could not stand or walk independently. Neither cerebellar ataxia nor autonomic system dysfunction was observed.

Laboratory tests showed 20 to 99 red blood cells per high power field and 5 to 9 granular casts per whole field in the urinary sediment, leading us to suspect nephritis. We therefore ran various serological tests to assess the likelihood of nephritis. The white blood cell count was high (11,000 cells/ μ L), and anemia was observed (hemoglobin: 8.6 g/dL). A coagulation test showed a prolonged activated partial thromboplastin time (43.6 s). Mild hepatic dysfunction was observed. Glucose tolerance was normal. Elevating C-reactive protein (CRP: 6.93 mg/dL) and normal procalcitonin (0.10 mg/dL) showed systemic inflammation without any bacterial infections. The immunoglobulin levels in the γ -globulin fraction and among complement proteins were normal. Antinuclear antibodies were not detected. Blood analysis revealed reduced levels of anti-DNA antibodies (<4 IU/mL) and anti-proteinase 3-ANCA (<1.0 U/mL) and a high level of MPO-ANCA (130.0 U/mL). The soluble interleukin-2 receptor (s-IL2R) level was 981 U/mL, and the rheumatoid factor level was 6 U/mL. Neither anti-Anti-Sjögren-syndrome-related antigen A nor antigen B antibodies were detected, and complement protein levels were within the normal range. Tumor marker levels were normal. The absence of serological abnormalities disproved our suspicion of nephritis and made us instead suspect a hepatitis B or C infection. We next ran several tests to assess the likelihood of hepatitis infection. The lack of any observed abnormalities led us to reject the possibility of a hepatitis infection.

An analysis of cerebrospinal fluid showed a cell count of 0 cells/ μ L, a protein concentration of 46 mg/dL, a glucose concentration of 62 mg/dL (simultaneous blood glucose: 116 mg/dL), and an s-IL2R concentration of <50.0 U/mL, all within normal ranges. No abnormalities were observed in electrocardiograms or chest and abdominal x-rays.

Brain MRI at 2 weeks after onset showed medial medullary infarction in diffusion-weighted imaging and T2-weighted imaging. When compared with MRI scans from the previous hospital, there was no obvious infarct enlargement or new infarct development (Fig. 1).

A carotid ultrasound did not show any clear plaque lesions on either side. Contrast-enhanced chest computed tomography (CT) did not show thickening or irregular width of the aortic vascular wall. Although minor pleural effusion was detected, chest CT revealed no lesion suggestive of vasculitis. From these findings, we denied suspicion of the large-vessel and/or medium-vessel vasculitis.

A bilateral limb nerve conduction study found no abnormalities. A neurological examination revealed left-dominant paresis of all four extremities, dysarthria, dysphagia, and enhanced tendon reflexes of the left extremities and MRI revealed right-side medial medullary infarction. Based on the detection of MPO-ANCA and systemic inflammation that was not attributable to

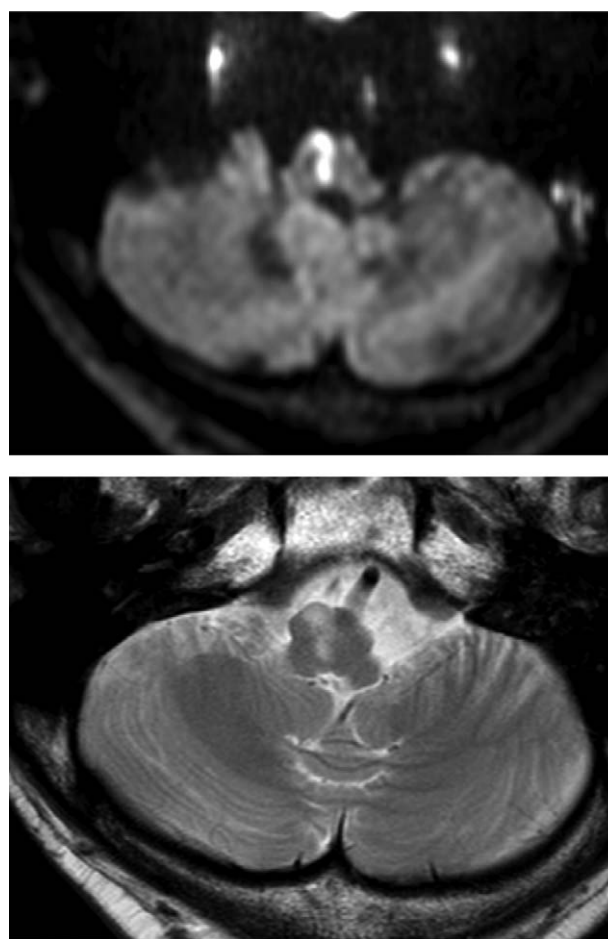


Figure 1. Brain magnetic resonance imaging at 2 weeks after onset showed a hyperintensity lesion in the right medial medulla oblongata on diffusion-weighted imaging and T2-weighted imaging. No clear infarct enlargement or suspicious new infarcts were observed in comparison with MRI scans taken at the previous hospital. We observed nonspecific high-signal intensity lesions in the deep white matter on T2-WI.

infection, we strongly suspected ANCA-associated vasculitis, but we could not perform a renal biopsy. We diagnosed cerebral lesion-limited ANCA-associated vasculitis with medullary infarction as an initial symptom. In screening for risk factors, carotid ultrasound imaging revealed no arteriosclerotic lesions, and we considered atherothrombotic brain infarction highly unlikely to be a risk factor, so the patient's favorably controlled hypertension was the only risk factor.

Because there was no adequate evidence to perform immunotherapy in patients with advanced age or in cases, such as ours, without lesions in other organs, we referred to Japanese guidelines,^[3] and chose steroid pulse therapy. We performed 2 courses of steroid pulse therapy on post-onset day 12 and prescribed 30 mg of orally administered prednisolone (PSL) for posttreatment. The inflammatory response (CRP >6 mg/dL) rapidly declined, and the MPO-ANCA level gradually decreased. PSL was continued at 30 mg/day until the MPO-ANCA and CRP level decreased to <10 U/mL and <0.03 mg/dL, respectively. On post-onset day 43, both MPO-ANCA and CRP levels had decreased.

Activities of daily living improved through rehabilitation. We performed gait training with a hybrid assistive limb (HAL) 5 times beginning a month after onset.^[4] The patient's Barthel

Table 1**Reported cases of the ANCA-related vasculitis that presented medullary infarction.**

Reports	Age/sex	Lesion	Affected organ	Onset of medullary infarction	ANCA antibody titer	Therapy
Chen et al ^[8]	72 M	Medial medullary	Renal; renal biopsy (+)	One month before renal dysfunction	P-ANCA; 788 U/mL	PE 4 times, Steroid pulse Tx + IVCY
Tarachenko et al ^[9]	41 M	Medial medullary	Renal; renal biopsy (+)	One week before renal dysfunction	C-ANCA; 100 U/mL	PE 5 times, Steroid pulse Tx + IVCY
Ozkul et al ^[10]	55 F	Lateral medullary	Auditory nerve, retina, lung; Nerve biopsy (+)	One day before fever	P-ANCA; 87.5 U/mL	Steroid pulse Tx, PSL 80 mg + IVCY
Bares et al ^[11]	52 F	Lateral medullary	Renal; renal biopsy (+)	Three month before renal dysfunction	C-ANCA; 320 times	PSL + IVCY
Fauset et al ^[12]	49 M	Lateral medullary	Lung, renal, peripheral nerve	One month after peripheral neurologic symptoms	C-ANCA; 160 times	Steroid pulse Tx, PSL 125 mg + IVCY
Present case	76 M	Medial medullary	Renal	Presenting symptom	P-ANCA; 130 U/mL	Steroid pulse Tx, PSL 30 mg

P-ANCA (= MPO-ANCA) = perinuclear antineutrophil cytoplasm autoantibodies, C-ANCA (= PR3-ANCA) = cytoplasmic antineutrophil cytoplasm autoantibodies, PE = plasma exchange, PSL = prednisolone, IVCY = intermittent pulse intravenous cyclophosphamide therapy.

index score improved from 35 at admission to 45 points before HAL training and 70 points after completion of the training. Although the patient still experienced distal-dominant muscle weakness, impaired sensation (impaired deep sensation and mildly impaired superficial sensation), and left femur-dominant dysesthesia, he became able to walk independently using a walker and was transferred to another hospital for further rehabilitation.

Our case report was waived from the ethical approval or institutional review board of University of Tsukuba hospital, based upon their policy to review all intervention and observational study except for a case report. Written informed consent was obtained from both patients for the publication of this manuscript and accompanying images.

3. Discussion

Primary vasculitis is classified into large-vessel, medium-vessel, and small-vessel types. In small-vessel vasculitis, lesions are present in the intraparenchymal small vessels such as small arteries, arterioles, capillaries, and venules. Cases are classified into immune complex-mediated and nonimmune complex-mediated groups. Nonimmune complex-mediated vasculitis includes ANCA-associated vasculitis, a disease group so-called because they share ANCAs as common disease markers. In 2012, the Chapel Hill Consensus Conference^[5] renamed and reclassified the subclasses of ANCA-associated vasculitis into microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. Although the common sites and mechanisms of cerebral infarction caused by ANCA-associated vasculitis have not been fully elucidated, Reichart et al,^[6] working before microscopic polyangiitis was established as a disease concept, observed infarcts in the deep white matter of the perforator region near a lacunar infarct in patients with polyarteritis nodosa.

Concerning the differential diagnoses of our case, we could exclude the diagnoses of IgA vasculitis and secondary vasculitis associated with collagen disease from the patient's medical history and blood findings, including autoantibodies. A diagnosis of polyarteritis nodosa was unlikely because there the patient presented no myalgia or arthralgia, and was ANCA-positive. Because there were no eye manifestations, erythema nodosum, oral aphtha, or pubic region ulcer, Behcet disease was excluded. PR3-ANCA was not detected, and there were no nose and ear

symptoms, including sinusitis or otitis media, and vasculitis lesions on chest CT; therefore, granulomatosis with polyangiitis was excluded, too. Finally, because he does not have asthma, allergic rhinitis, eosinophilia, or IgE elevation until now, a diagnosis of eosinophilic granulomatosis with polyangiitis was unlikely.

Because CRP and MPO-ANCA titer moved parallel to the disease activity, and skin lesions associated with livedo reticulata and renal dysfunction were observed, we diagnosed this case as cerebral lesion-limited ANCA-associated vasculitis with the exclusion of other possible vasculitis.

There are some limitations about the diagnosis of our case. First, the diagnosis was not confirmed pathologically; second, no abnormalities were found in main target organs, such as the kidneys or lungs.

Medullary infarction is less common than cerebral infarction. Lateral medullary infarction accounts for no >2.5% of all reported cerebral infarction cases, and medial medullary infarction accounts for no >1%.^[1] In addition, Toyoda et al^[7] reported observing 11 cases (0.52%) of medullary infarction among 2130 brain infarction cases. The risk factors for medial medullary syndrome (MMS) and lateral medullary syndrome (LMS)^[1,2] include hypertension (seen in 64%–89% of MMS patients and 75% of LMS patients, respectively), diabetes (25%–27% and 37%, respectively), recent smoking history (6.8%–25% and 25%, respectively), and dyslipidemia (20% and 12%, respectively). Vasculitis is an extremely rare cause.

Only 5 cases of ANCA-associated vasculitis with medullary infarction have been previously reported (Table 1).^[8–12] The patients in these cases were slightly younger (range: 41–72 years) than ours. The lesion sites included the medial (n = 2) and lateral (n = 3) parts of the medulla oblongata. Except for nonspecific symptoms such as fever, medullary infarction was the initial symptom in most cases, as in ours. In all the patients with renal dysfunction symptoms, these occurred or rapidly progressed after the infarction developed. All patients received strong immunotherapy combined with steroid and cyclophosphamide (CY) treatment, which resulted in favorable outcomes for all except one with severe renal dysfunction.

Methotrexate or mycophenolate mofetil with glucocorticoid is recommended as the standard therapies for ANCA-associated vasculitis.^[13] As shown in the Table 1, CY and plasma exchange were combined with steroids in cases of medullary infarction caused by ANCA-associated vasculitis with previous renal and/or

lung involvement. However, there are 2 reports of ANCA-associated vasculitis causing an isolated (without previous renal and/or lung involvement) cerebrovascular lesion, which was treated with steroid therapy alone.^[14,15] As our patient was an elderly patient lacking severe lesions in other organs, we followed the Japanese guidelines^[3] and administered steroids alone, thus obtaining a successful outcome.

4. Conclusion

When systemic inflammation is observed in cases of medullary infarction, ANCA-associated vasculitis should be considered a potential cause, and steroid pulse therapy should be promptly administered.

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