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Anti-neutrophil cytoplasmic antibody–associated vasculitis complicated with diffuse alveolar haemorrhage and central nervous system vasculitis

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Abstract

Diffuse alveolar haemorrhage and central nervous system vasculitis are life-threatening complications of anti-neutrophil cytoplasmic antibody-associated vasculitis. The simultaneous occurrence of diffuse alveolar haemorrhage and central nervous system vasculitis is a rare presentation of antibody-associated vasculitis. Its diagnosis by histopathology is difficult because biopsy is difficult to perform, and urgent treatment is needed. We report a case of a Japanese man with diffuse alveolar haemorrhage and central nervous system vasculitis associated with antibody-associated vasculitis. New classification criteria may be needed for diffuse alveolar haemorrhage and central nervous system vasculitis associated with systemic vasculitis. When antibiotic-resistant atypical bilateral pneumonia is noted in the acute phase of a cerebral stroke, with elements suggestive of vasculitis, clinicians should be aware that diffuse alveolar haemorrhage and central nervous system vasculitis may occur simultaneously.

Keywords

Anti-neutrophil cytoplasmic antibody-associated vasculitis, diffuse alveolar haemorrhage, central nervous system vasculitis

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Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) is a type of primary systemic vasculitis that predominantly affects the small systemic vessels and is characterised by the presence of ANCAs in the serum.[1,2]

AAV has protean manifestations in various organs, and the disease spectrum ranges from indolent to organ- or life-threatening conditions.[2] Life-threatening dysfunctions of AAV are often observed in the lungs and kidneys.[2–4] Thus, diffuse alveolar haemorrhage (DAH), interstitial pneumonia, and renal vasculitis associated with AAV can be causes of death.[3] Particularly, the prognosis of patients with DAH is poorer than that of patients with other manifestations of AAV.[4] Furthermore, central nervous system (CNS) vasculitis is a rare but alarming manifestation of this condition.[5,6] Here, we report a case of a Japanese man with AAV complicated with DAH and CNS vasculitis.

Case report

A 76-year-old Japanese man was admitted to our hospital due to acute respiratory failure and weakness of both lower extremities. One year before admission, he was diagnosed with interstitial pneumonia associated with positive myeloperoxidase-anti-neutrophil cytoplasmic antibody (MPO-ANCA) measured by enzyme-linked immunosorbent assay (ELISA) in another hospital (37.2 U/mL; normal range = 3.5 U/mL). During this period, he did not receive immunosuppressive

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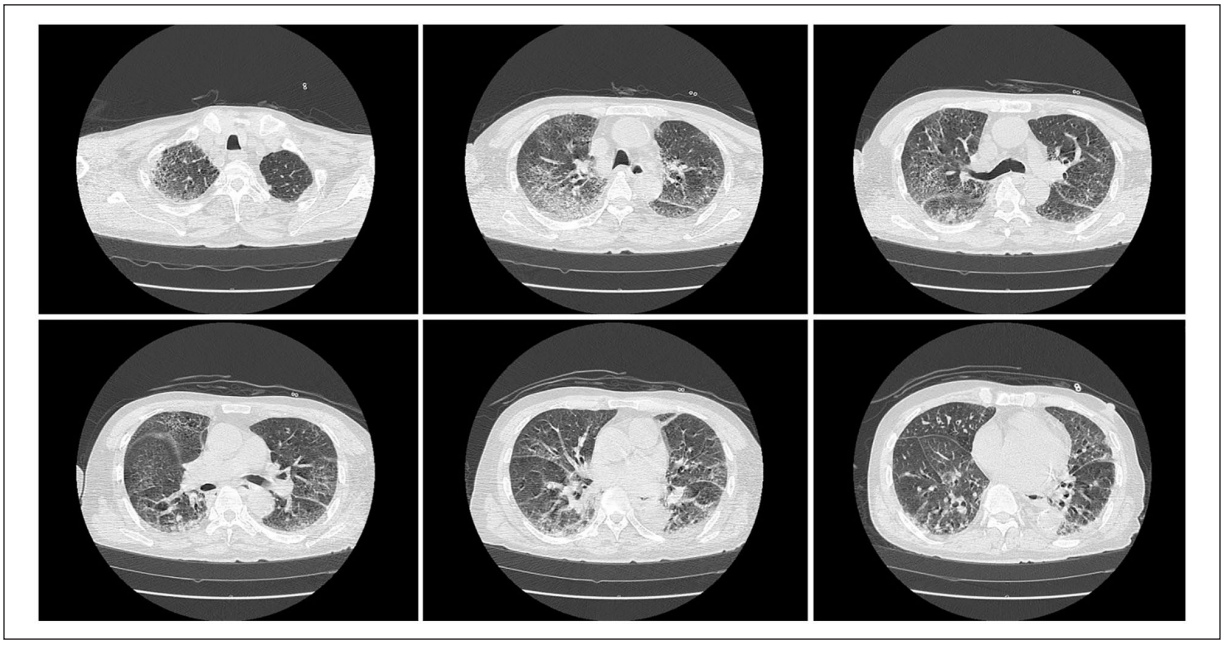

Figure 1. Chest computed tomography performed in the former hospital reveals diffuse bilateral ground-glass opacities.

therapy because the activity of interstitial pneumonia was considered low. In addition, he had a history of hypertension, Parkinson's disease associated with cognitive/memory dysfunction, atherothrombotic brain infarction treated with right carotid artery stent placement, and chronic obstructive pulmonary disease. He was administered some drugs, including benserazide hydrochloride, cilnidipine, and pitavastatin; however, he did not take drugs that could induce AAV. One week before the current admission, he was taken to the former hospital due to acute respiratory failure and weakness of both lower extremities. There, he was treated with an antibiotic agent (ceftriaxone) and prednisolone (PSL, 15 mg/day). However, his respiratory condition did not improve, and he was transferred to our hospital.

On admission, his vital signs were as follows: body temperature, 37.6°C; respiratory rate, 25 breaths/min; SpO_2, 95% in 4 L/min of oxygen administered via a nasal cannula. A saddle nose deformity and skin abnormalities, such as purpura or livedo reticularis, were not observed. Neurological examination revealed weakness of both lower extremities (grades 4−/4−, 4−/3+, and 4−/4− for the iliopsoas, quadriceps, and tibialis anterior, respectively) and exaggerated lower extremity tendon reflexes. Laboratory investigations revealed an elevated serum C-reactive protein (CRP) level (6.75 mg/dL). The serum MPO-ANCA and proteinase-3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) levels, as measured by ELISA, were 12.1 and 4.1 U/mL, respectively (normal range for both, 3.5 U/mL). An indirect immunofluorescence assay for ANCA was not performed on admission. In addition, a complete blood cell examination revealed normocytic anaemia (haemoglobin, 7.6 g/dL). The serum haemoglobin level on admission to the former hospital was 10.7 g/dL, suggesting acute anaemia due to bleeding. Leucocytes were increased (155.3×10^8/L), and eosinophils accounted for 1.5% of leucocytes. His liver function showed no abnormality. Serum levels of Krebs von den Lungen (KL-6) and creatine kinase were slightly elevated (642 U/mL, normal range = 499 U/mL and 252 U/L, normal range = 248 U/L, respectively). The antinuclear antibodies titre was 1:320, with a homogeneous pattern. The following antibodies were negative: DNA, Sm, U1-RNP, SS-A, Scl-70, CCP, and GBM. Atypical and blast cells were not observed, and he tested negative for anticardiolipin IgG and lupus anticoagulant. Although the serum creatinine levels were elevated (1.28 mg/dL), urinalysis did not reveal urinary protein or abnormal urinary casts. These results suggested that his renal dysfunction was caused by dehydration and poor oral intake rather than glomerulonephritis. Cerebrospinal fluid (CSF) analysis was not conducted because he found maintaining a posture difficult due to dyspnoea.

Chest computed tomography revealed diffuse bilateral ground-glass opacities (Figure 1). Although magnetic resonance angiography did not reveal any brain blood vessel occlusion, brain magnetic resonance imaging (MRI) revealed multiple acute brain infarcts (Figure 2). Spinal MRI was not conducted on admission, and echocardiographic findings were not suggestive of infective endocarditis.

We consulted neurologists and pulmonologists in our hospital and clinically diagnosed him with AAV associated with DAH and CNS vasculitis based on the clinical findings. We concluded that his muscle weakness was caused by nerve damage due to CNS vasculitis (multiple acute brain infarcts). He underwent a 3-day course of steroid pulse therapy (methylprednisolone, 1 g/day) and subsequent oral PSL therapy

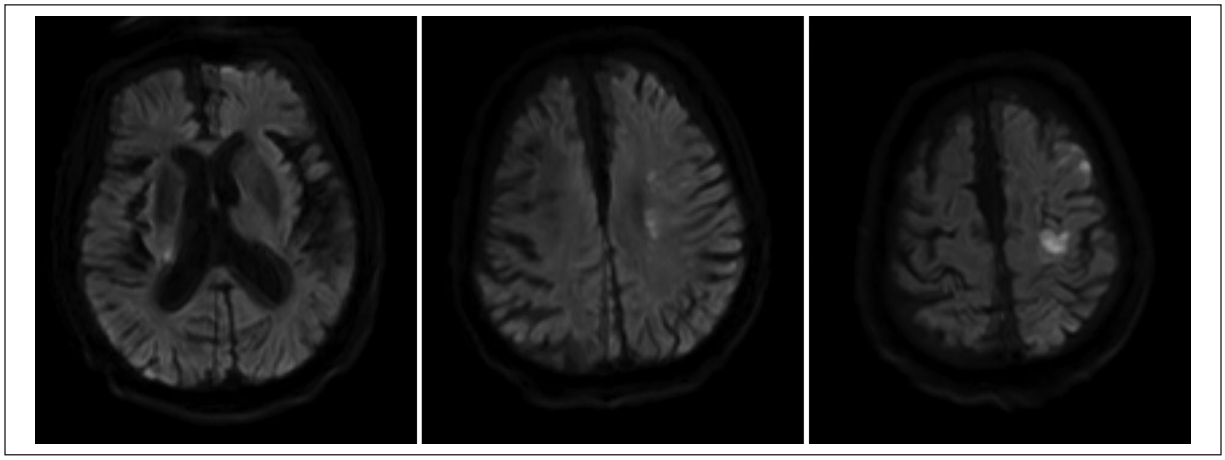

Figure 2. Brain magnetic resonance imaging with diffusion-weighted imaging reveals multiple acute brain infarcts.

(initial dose, 60 mg/day) with intravenous cyclophosphamide (IVCY). However, he suffered from aspiration pneumonia and cytomegalovirus infection, making the continuous administration of IVCY difficult. Therefore, cyclophosphamide was changed to azathioprine following a second course of IVCY; after these treatments, his respiratory condition improved. The PSL dose was gradually tapered, and his muscle strength improved slightly after treatment (grades 4−/4−, 4/4−, and 5−/5− for the iliopsoas, quadriceps, and tibialis anterior, respectively). However, he needed to continue rehabilitation and was finally transferred to the other hospital, where the PSL doses were continuously reduced. Three months after the initiation of steroid therapy, the PSL dose was reduced to 7.5 mg/day without any symptoms suggestive of a relapse of systemic vasculitis.

Discussion

In this case, DAH and CNS vasculitis were simultaneously observed in a patient with ANCA seropositivity. A flare in vasculitis is often accompanied by an increase in the serum ANCA level.[7] However, the patient's serum MPO-ANCA level was lower at admission than at the evaluation prior to this admission. We hypothesise that this decrease in the MPO-ANCA level was affected by pre-treatment with PSL in the former hospital.

The co-occurrence of DAH and CNS vasculitis is a rare finding in AAV, with only a few reported case.[8,9] DAH is characterised by new pulmonary infiltrates on chest radiography and acute anaemia. Although haemoptysis is also a characteristic finding of DAH, approximately one-third of the patients present without it.[10] Because imaging findings of DAH involve several differential diagnoses, including pulmonary oedema, thromboembolism, infection, coagulopathy and uraemia, bronchoscopy with bronchoalveolar lavage (BAL) is helpful for confirming DAH.[11] If BAL cannot be performed, excluding these differential diagnoses with certainty is important. CNS vasculitis causes ischaemic infarctions, which often appear as isolated or multiple lesions located in the white matter, as the distal vessels are predominantly affected.[5] Differential diagnoses of CNS vasculitis include a wide variety of conditions ranging from embolic diseases to coagulation disorders.[12] In CNS vasculitis associated with systemic vasculitis, serum findings often reveal an acute inflammatory response, such as an increased CRP level. Conversely, in primary angiitis of CNS, while serum findings are usually normal, CSF analysis reveals inflammatory findings.[12] It was reported that cerebral microbleeds (CMBs) on brain MRI might be a marker of cerebral small-vessel disease.[13] However, CMBs are also observed in various disorders such as Alzheimer's disease, cerebral amyloid angiopathy and trauma.[14] It is difficult to detect findings specific to CNS vasculitis, especially in relation to small-sized vessels predominantly disordered by AAV. Thus, it is important to exclude differential diagnoses of CNS vasculitis as well as DAH.

The imaging and clinical findings in our case were compatible with those of DAH and CNS vasculitis. Furthermore, our case did not present with any findings suggestive of the abovementioned differential diagnoses of DAH and CNS vasculitis. Therefore, we clinically diagnosed the patient with systemic vasculitis; however, his poor general condition and pre-treatment with PSL made it difficult to establish a definitive pathological diagnosis. Our case was defined as 'unclassifiable vasculitis' as per the Watts criteria for the classification of vasculitis, owing to the lack of histologic confirmation.[15]

Our case suggests two important facts. First, although DAH and CNS vasculitis are manifestations of AAV, they sometimes occur without other involvements, as observed in our case. In addition, DAH and CNS vasculitis are emergency conditions, which require urgent treatment. Although using the Watts criteria is an excellent method for classifying primary systemic vasculitis, accurately classifying patients with DAH or CNS vasculitis is difficult. Indeed, a previously reported case of AAV associated with DAH and CNS was

not classified according to the Watts criteria and was diagnosed with microscopic polyangiitis (MPA) according to the Japanese local criteria for MPA.[8] Therefore, new classification criteria are needed for AAV associated with DAH or CNS vasculitis.

Second, although the co-occurrence of DAH and CNS vasculitis is a rare presentation of AAV, some patients who suffer from acute respiratory failure after cerebral stroke may have DAH. Generally, aspiration pneumonia is a frequent cause of acute respiratory failure in post-stroke patients. However, clinicians should consider the possibility of a simultaneous occurrence of DAH and CNS vasculitis when they encounter antibiotic-resistant atypical bilateral pneumonia during the acute phase of cerebral stroke with elements suggestive of vasculitis (e.g. young age, unexplained aetiology, and concomitant involvement of several vascular territories).

Conclusion

New classification criteria may be needed for DAH and CNS vasculitis associated with systemic vasculitis. In addition, when antibiotic-resistant atypical bilateral pneumonia is noted in the acute phase of a cerebral stroke, with elements suggestive of vasculitis, clinicians should be aware that DAH and CNS vasculitis may occur simultaneously.

Declaration of conflicting interests

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Ethical approval

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Informed consent

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