Case report

A case of granulomatosis with polyangiitis (Wegener's granulomatosis) manifested with asymptomatic intracerebral hemorrhage

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summary

A 46-year-old man, who had had sinusitis, developed bilateral omalgia, petechiae on his lower extremities and a congested right eye. A blood test detected elevated serum C-reactive protein level. Computed tomography incidentally found an acute lesion of thalamic hemorrhage without neurological symptoms and no specific therapy was given at the time. Thereafter, he developed vertigo, vomiting and pneumonia for which antibiotics were ineffective. He was referred and admitted to our hospital. Further, aural and renal lesions, and presence of serum proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) confirmed his diagnosis of granulomatosis with polyangiitis (Wegener's) (GPA). With corticosteroid and cyclophosphamide therapy, his symptoms disappeared in two months along with faded PR3-ANCA. Afterward he showed neither new cerebral lesion nor symptom. This is a rare case of GPA manifested with asymptomatic intracerebral hemorrhage. It should be noted that GPA could cause various manifestations in central nervous system such as a fatal or an asymptomatic hemorrhagic lesion, which might respond to immunosuppressive therapy.

Key words—granulomatosis with polyangiitis; Wegener's granulomatosis; intracerebral hemorrhage; cerebral hemorrhage; antineutrophil cytoplasmic antibody

Introduction

Granulomatosis with polyangiitis (Wegener's) (GPA), an alternative name for Wegener's granulomatosis¹, is a multisystemic, granulomatous and necrotizing small-vessel vasculitis. It affects not only the respiratory tract, lower airway and kidneys but also skin, joints, eyes and the nervous system. Before the institution of effective immunosuppressive therapy, the prognosis of GPA was very poor. The overall mortality in GPA patients was 4.7 times higher than that in the general population². The disease manifestations of GPA are heterogeneous and the prognosis varies considerably. Some GPA patients can develop manifestations in central nervous system including intracranial hemorrhage, which are often fatal^{3,4}. We present a case disclosing diversity of GPA manifestations.

Case Report

A 46-year-old man was admitted to a hospital with bilateral omalgia, petechiae on his lower extremities and a congested right eye. His past history included only sinusitis and it was inactive lately. Plain X-ray

of the shoulder and neck demonstrated no abnormal findings. A blood test detected elevated serum C-reactive protein (CRP) level. Besides the arthritis, computed tomography (CT) scan of the head was also performed as a general screening, which incidentally detected an acute lesion of right thalamic hemorrhage (Fig. 1). He had neither paralysis of the upper extremities nor any other neurological disorders by the physical examination. His blood pressure had been normal and further, had no disorder associated with embolism (e.g., valvular heart disease, arrhythmia, sepsis or infectious endocarditis). No specific therapy was given to him and his symptoms continued. The four months later, petechiae and arthritis in bilateral shoulder and knee joints deteriorated. No new lesion was found by head CT scan. A further two months later, he admitted to the hospital again with vertigo, tinnitus and vomiting. CT scan showed abnormalities in the lungs and he was diagnosed as pneumonia. He received antibiotics but they did not improve his symptoms, which was the reason why he was referred to our hospital. On admission, he still suffered from non-destructive polyarthritis and petechiae on bilateral upper and lower extremi-

Fig. 1 Computed tomography scan of the head detected right thalamic hemorrhage.

Fig. 2 Petechiae on the lower extremity.

ties (Fig. 2). Blood pressure was 130/70 mmHg and body temperature was 37.7°C. Physical examinations and neurological tests presented no remarkable findings. Urinalysis showed proteinuria and hematuria. White blood cell count was 9780/mm³, serum CRP was 12.6 mg/dl and proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) titer was 102 EU, whereas serum transaminase and creatinine levels were normal. In addition to bacteriological examinations, immunological examinations including antinuclear antibody, antiphospholipid antibody, and myeloperoxidase (MPO)-ANCA were negative. Chest CT scan demonstrated diffuse ground-glass opacity in the right upper lung. Magnetic resonance (MR) angiograph of the head was normal, while MR imaging and CT scan of the head detected an old hemorrhagic lesion at right thalamus and bilateral sinusitis. Skin biopsy at a petechia revealed the subepidermal blister and neutrophil infiltration at small vessels in the dermis. Deposition of fibrin was

Fig. 3a Histological examination of the cutaneous tissue at a petechia shows neutrophil infiltration at a small vessel in the dermis and deposition of fibrin in blood vessel walls (original magnification $\times 100$).

Fig. 3b Histological examination of a renal biopsy specimen shows focal, segmental and necrotizing crescentic glomerulonephritis (original magnification $\times 400$).

seen in blood vessel walls (Fig. 3a). Renal biopsy found focal, segmental and necrotizing crescentic glomerulonephritis without immunoglobulin deposition (Fig. 3b). Furthermore, he developed deafness due to tympanitis, hemoptum and episcleritis. With the diagnosis of GPA, corticosteroid therapy (methylprednisolone 1 g daily for 3 days followed by prednisolone 80 mg daily) was given and it improved his arthritis, tympanitis and episcleritis. Chest X-ray revealed decreased reticular shadow in 10 days after the induction therapy. Additionally, monthly intravenous cyclophosphamide therapy was administered. The one month later, petechiae tended to disappear obviously and PR3-ANCA titer fell to 29 EU. The two months later after the induction therapy, chest CT confirmed no abnormal shadow and PR3-ANCA titer became negative. Corticosteroid could be

reduced to under 20 mg in 6 months after the induction therapy. Afterward brain CT or MR imaging detected only the primary lesion as an old hemorrhage and did no new lesions.

Discussion

This is a rare case of GPA developed with asymptomatic intracerebral hemorrhage (ICH). Although pathological surveys did not detect the specific necrotizing granulomatous vasculitis, his diagnosis of GPA is more reliable than that of microscopic polyangiitis because of his manifestations containing sinusitis, episcleritis, and tympanitis together with presence of serum PR3-ANCA, fulfilling the diagnostic criteria of the Japanese Research Group, Ministry of Health, Labour, and Welfare of Japan, for Wegener's granulomatosis⁵⁾.

Asymptomatic intracerebral hemorrhage (ICH) is defined as ICH without sudden focal signs, namely, classical neurological findings including motor or sensory disturbance, or aphasia. It is reported that only 0.6% of MR imaging examinations detected asymptomatic ICH. Most cases with primary asymptomatic ICH were men 50 years or older, who all had hypertension⁶⁾. Another study from Japan demonstrated that MR imaging for healthy adults found ICH lesions in 2.2% of subjects and revealed that age over 65 and diastolic hypertension were risk factors for ICH⁷⁾. Our case had no risk factors for ICH such as hypertension, diabetes or smoking, and had no aneurysm or vascular malformation in the brain. Additionally, his fresh hemorrhagic lesion of the thalamus coincided with manifestations of GPA such as arthritis and petechiae. Therefore, his asymptomatic ICH is more likely to be secondary to GPA.

It is described that the frequency of neurologic involvement in GPA was as high as 54%⁸⁾, and that of cerebral vasculitis as 3 to 5%⁹⁾. Neurologic complications of GPA are classified into three subsets, which include encroachment from nasal or paranasal granulomas, direct granulomatous involvement of nervous system, and vasculitis of the nervous system⁸⁾. Indeed cerebral vasculitis has been histopathologically demonstrated in patients with GPA^{8,10)}, but it is difficult to identify the pathogenesis of every case because biopsy of the lesion or autopsy is necessary when cerebral imaging methods cannot detect the specific findings of vasculitis such as irregularity of arterial walls or obstruction of arteries¹¹⁾. In our case CT or MR imaging could find neither vasculitis nor granuloma as most cases with GPA and ICH^{3,4)}.

Because only a microscopic destruction of a blood vessel by vasculitis or by a minute invasive granuloma could result in ICH, it would be common that ICH due to GPA presents no specific findings with cerebral imaging methods. In either pathogenesis, immunosuppressive therapies can be effective if the lesion is associated with GPA. As for our case, at least, recurrence including a cerebral lesion might be prevented by the therapies for GPA.

The prognosis of patients with ICH complicating GPA was so poor that nearly a half of them were fatal^{3,4)}. The reason is, first, that ICH is a serious medical emergency for which efficacious therapy is limited depending on the location and size of the lesion. Second, no immunosuppressive therapy was formerly available for GPA³⁾. Third, the development of central nervous vasculitis with hemorrhage sometimes does not correlate with the disease activity in other organs⁴⁾. The preferable prognosis in our case was probably due to the size and activity of the lesion which was neither massive nor dynamic.

In addition to a rare central nervous involvement, asymptomatic ICH with GPA is unique. It means that developing GPA can yield ICH even early in the disease course and/or without nervous symptoms, and then cerebral imaging as screening in patients with GPA can find previously unrecognized, clinically silent lesions. It would be difficult to make diagnosis of GPA if the primary lesion was in central nervous system like our case, but the following systemic manifestations would give clues to diagnosis. We should consider the association between GPA and ICH when we treat patients with ICH who has multiple organ involvements suggesting GPA or has no risk factors for ICH, as their ICH might be secondary to GPA and could be treatable.

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References

- 1) Falk, R. J., et al. : Granulomatosis with polyangiitis (Wegener's) : an alternative name for Wegener's granulomatosis. *Arthritis. Rheum.*

- 63 : 863–864, 2011.
- 2) Matteson, E. L., et al. : Long-term survival of patients with Wegener's granulomatosis from the American College of Rheumatology Wegener's Granulomatosis Classification Criteria Cohort. *Am. J. Med.* **101** : 129–134, 1996.
 - 3) Kishimoto, M., Arakawa, K. C. : A patient with Wegener's granulomatosis and intraventricular hemorrhage. *J. Clin. Rheumatol.* **9** : 354–358, 2003.
 - 4) Memet, B., et al. : Wegener's granulomatosis with massive intracerebral hemorrhage : remission of disease in response to rituximab. *J. Clin. Rheumatol.* **11** : 314–318, 2005.
 - 5) Ozaki, S. : ANCA-associated vasculitis : diagnostic and therapeutic strategy. *Allergol. Int.* **56** : 87–96, 2007.
 - 6) Nakajima, Y., et al. : Asymptomatic cerebral hemorrhage detected by MRI. *Rinsho Shinkeigaku.* **31** : 270–274, 1991.
 - 7) Takahashi, W., et al. : Clinical characteristics in normal healthy adults with microbleeds on echo-planar gradient-echo T2-weighted MRI. *Jpn J Stroke.* **26** : 357–363, 2004.
 - 8) Drachman, D. A. : Neurological complications of Wegener's granulomatosis. *Arch. Neurol.* **8** : 145–155, 1963.
 - 9) Holle, J. U., Gross, W. L. : Neurological involvement in Wegener's granulomatosis. *Curr Opin Rheumatol.* **23** : 7–11, 2011.
 - 10) Seror, R., et al. : Central nervous system involvement in Wegener's granulomatosis. *Medicine.* **85** : 54–65, 2006.
 - 11) Yamashita, Y., et al. : Cerebral vasculitis secondary to Wegener's granulomatosis : computed tomography and angiographic findings. *J Comput Tomogr.* **10** : 115–120, 1986.