

[CASE REPORT]

Granulomatosis with Polyangiitis Complicated by Hypertrophic Pachymeningitis Presenting with Simultaneous Multiple Intracerebral Hemorrhages

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Abstract:

Central nervous system (CNS) involvement in granulomatosis with polyangiitis (GPA), including pachymeningitis and CNS vasculitis, is uncommon. Although intracerebral hemorrhage (ICH) has been reported in GPA, simultaneous multiple ICH (SMICH) is rare. We describe the case of a 50-year-old woman with a history of a limited form of GPA with chronic pachymeningitis who presented with acute-onset headache accompanied by nausea and vomiting, and who developed consciousness impairment. Computed tomography revealed bilateral subcortical ICH. Sinus thrombosis was not apparent on angiography. The patient was treated with high-dose corticosteroid therapy. The cause of the steroid-responsive SMICH in this case was unknown, but it might have been CNS vasculitis. Patients with GPA may present with SMICH, which is considered an indication for immunosuppressive therapy.

Key words: granulomatosis with polyangiitis, pachymeningitis, multiple intracerebral hemorrhages

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Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is characterized by anti-neutrophil cytoplasmic antibody (ANCA)-associated granulomatous vasculitis of small and medium-sized vessels, and mainly affects the upper and lower respiratory tracts and kidneys (1).

Previous studies have reported that the prevalence of neurological abnormalities of the central nervous system (CNS) and peripheral nervous system of patients with GPA ranges from 29% to 54% (2-5). The most common form of peripheral nervous system involvement is vasculitic neuropathy, which typically presents as mononeuritis multiplex. The main CNS manifestations of GPA include: (1) meningeal inflammation presenting as pachymeningitis with headaches and cranial neuropathies (6); and (2) vasculitis of the cerebral arteries (CNS vasculitis) leading to ischemic infarction, intracerebral or subarachnoid hemorrhage, and arterial and venous thrombosis.

Intracerebral hemorrhage (ICH) is reported to occur in up to 6% of patients with GPA and CNS abnormalities (5). However, the simultaneous occurrence of ICHs in different vascular territories [simultaneous multiple ICH (SMICH)] is rare (7-10). We herein describe the case of a 50-year-old woman with a history of GPA and chronic pachymeningitis who presented with simultaneous multiple intracerebral hemorrhage (SMICH), and discuss the indications for immunosuppressive treatment in patients with GPA and SMICH.

Case Report

At 48 years of age the patient developed intractable serous otitis media and left-sided headache, followed by trigeminal neuralgia and facial nerve paralysis on the left side. Brain magnetic resonance imaging (MRI) revealed hypertrophic pachymeningitis. A test for ANCA to myeloperoxidase (MPO-ANCA) was positive (74 U/mL; normal value <3.5), while a test for ANCA to proteinase 3 (PR3-ANCA) was negative. Corticosteroid treatment was initiated

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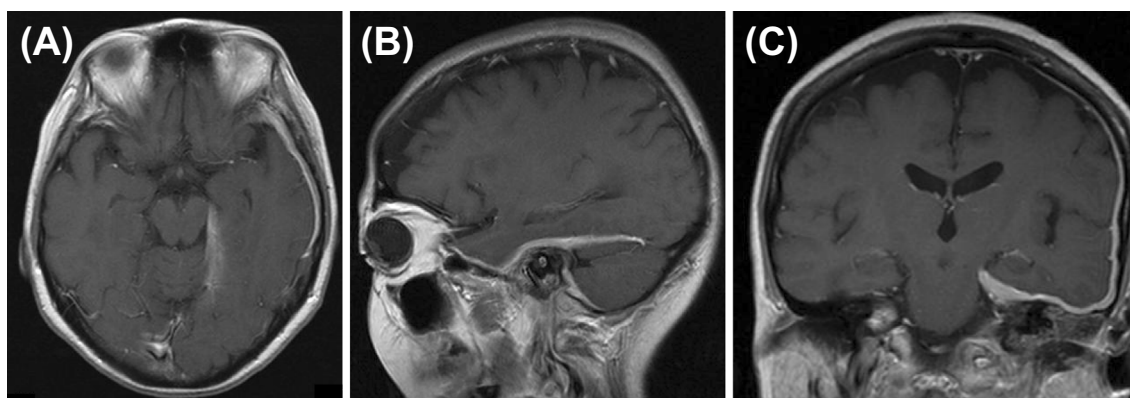


Figure 1. Axial (A), sagittal (B), and coronal (C) T1-weighted magnetic resonance imaging of the brain with gadolinium enhancement showing dural thickening with diffuse gadolinium-enhancement along the left tentorium and left cerebellar surface in the left temporoparietal region. This finding was consistent with hypertrophic pachymeningitis.

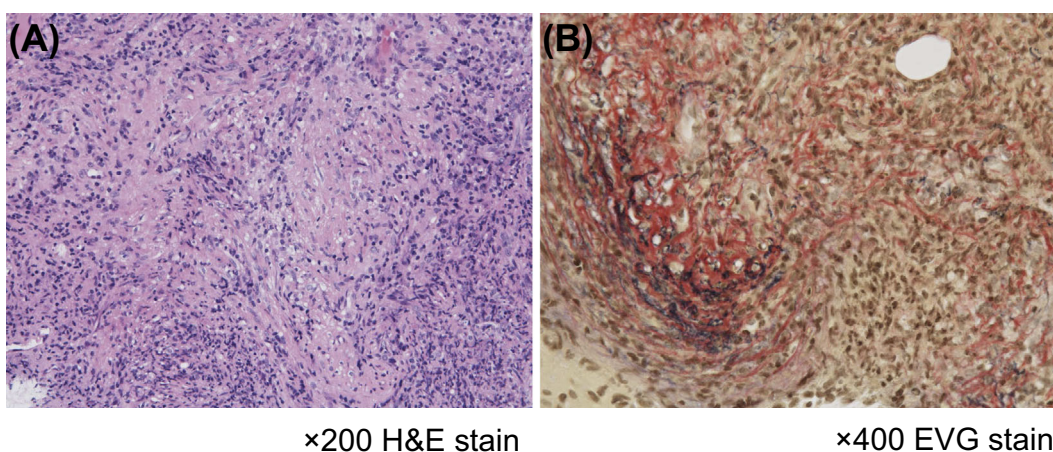


Figure 2. A histopathological examination of a nasal mucosal biopsy specimen revealed (A) necrotizing granulomatous inflammation with central necrosis and mixed inflammatory infiltrate (200 \times , Hematoxylin and Eosin staining), and (B) fragmentation of the elastic lamina, suggestive of destruction of the blood vessels (vasculitis; 400 \times , EVG staining). EVG: Elastica van Gieson

with prednisolone (40 mg/day). This promptly improved her symptoms. This was gradually tapered to a maintenance dose of 10 mg/day.

At 49 years of age, the patient presented with a 2-month history of headache and nausea, followed by the recurrence of left-sided trigeminal neuralgia and facial nerve paralysis. Brain MRI revealed diffuse thickening and the gadolinium enhancement of the dura mater, which was consistent with a recurrence of pachymeningitis (Fig. 1). A biopsy of the nasal mucosa revealed necrotizing granulomatous inflammation (Fig. 2), which established the diagnosis of a limited form of GPA. The prednisolone dose was increased to 40 mg/day; however, the response was insufficient. Monthly intravenous cyclophosphamide therapy (IVCY) was therefore initiated and administered 3 times (at doses of 600 mg, 800 mg, and 800 mg), after which she declined further IVCY because of gastrointestinal side effects. In view of the patient's lack of response to 3 months of IVCY, she was treated with intravenous methylprednisolone (1,000 mg daily, for 3 days), and

IVCY was replaced with methotrexate (15 mg/week), which ameliorated the neurologic symptoms. She continued to receive low-dose weekly methotrexate as maintenance therapy, and the dose of prednisolone was tapered to 4 mg/day.

At 50 years of age, the patient again presented with acute-onset headache accompanied by nausea. Brain computed tomography (CT) showed no abnormalities other than the widening of the Sylvian fissures and bilateral atrophy of the frontal lobes, which was noticeable in comparison with brain CT images performed 2 years earlier (Fig. 3). However, she developed consciousness impairment (Japan coma scale; III-100) on the following day. A physical examination revealed no remarkable findings other than consciousness impairment and disorientation. The patient's inflammatory marker levels were elevated (C-reactive protein 2.5 mg/dL). Tests for both PR3-ANCA and MPO-ANCA were negative. Brain CT showed bilateral frontal subcortical ICH (Fig. 4). Transthoracic echocardiography did not reveal a cardiac embolic source. Cerebral angiography did not show any evi-

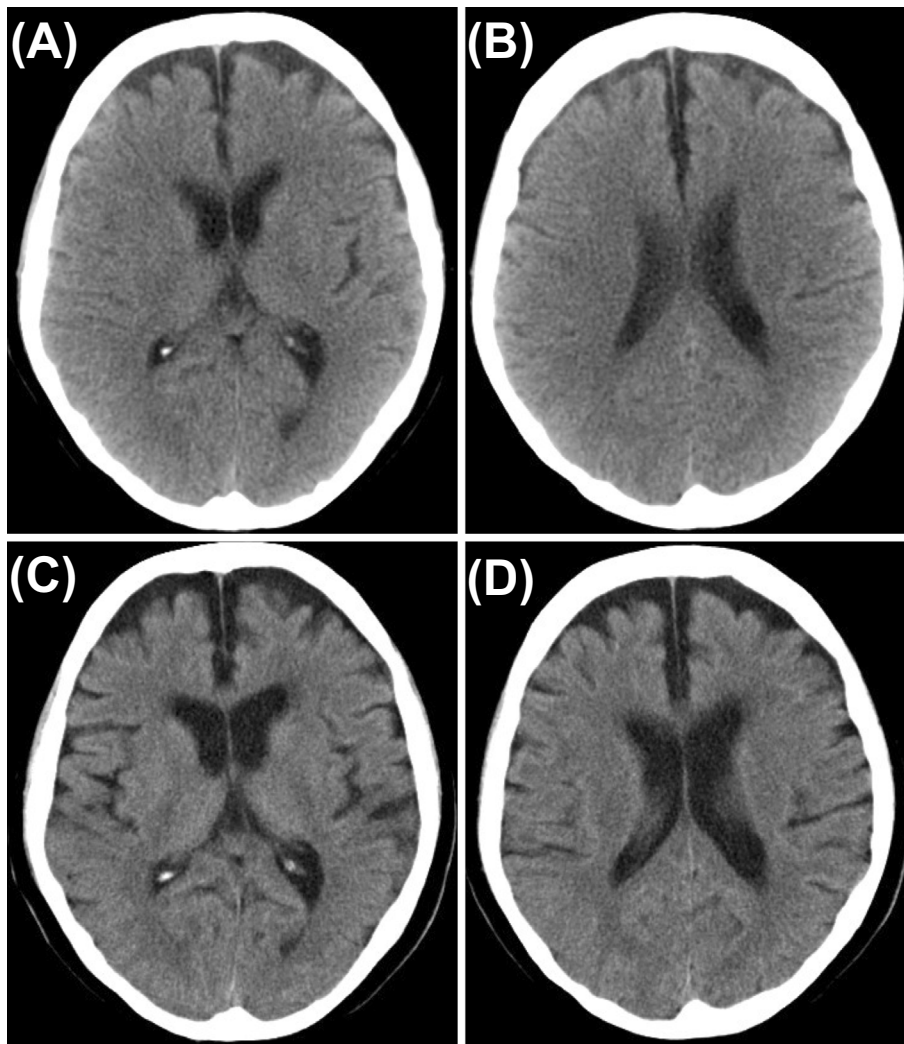


Figure 3. Brain computed tomography showing the progression of cerebral atrophy and the development of multiple and simultaneous intracranial hemorrhage. Computed tomography of the brain was performed (A, B) 2 years before and (C, D) one day before the development of simultaneous intracranial hemorrhage.

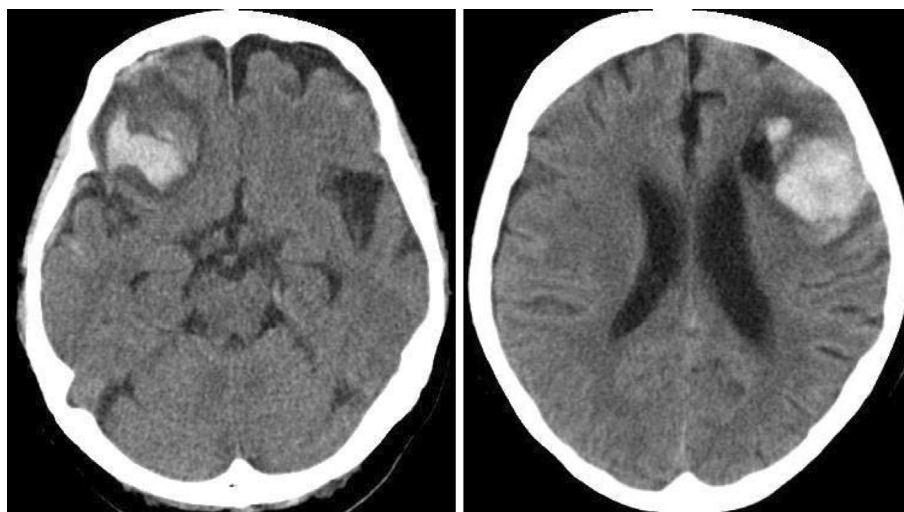


Figure 4. Brain computed tomography showing bilateral frontal subcortical intracerebral hemorrhages.

dence of vascular irregularities, stenosis, intracerebral aneurysm, or sinus thrombosis. T2*-weighted brain MRI did not show any low-signal intensity microfoci outside the cerebral hemorrhage lesions. The patient was treated with intravenous methylprednisolone (500 mg, daily for 3 days) followed by oral prednisolone (30 mg/day). Although mild higher brain dysfunction remained, she was discharged after tapering the dose of prednisolone to 15 mg/day.

Discussion

We herein describe the case of a 50-year-old woman with GPA and a history of hypertrophic pachymeningitis who developed consciousness impairment and SMICH that responded to high-dose corticosteroid therapy.

The simultaneous occurrence of ICH in different arterial territories is an uncommon event (8-10). Stemer et al. defined SMICH as two discrete ICHs with similar density profiles on initial CT that occurred simultaneously or within 24 hours of the first identified ICH (7). SMICH can be categorized as primary (spontaneous) or secondary (caused by an underlying condition). The two main causes of primary SMICH are hypertensive vasculopathy and cerebral amyloid angiopathy (10), but it is not known if there are other cause (s). Multiple etiologies have been suggested for secondary SMICH. Hematologic abnormalities are the most common cause, followed by the concomitant use of anticoagulants or antithrombotic drugs, venous sinus thrombosis, vasculitis, cerebral metastasis, and cardiopulmonary resuscitation (7, 11-13).

With regard to the underlying causes of SMICH, our patient had no history of hypertension and did not use anticoagulants or antithrombotic drugs. Although cerebral hemorrhage after the recanalization of cerebral embolism was one of the differential diagnoses in this patient, transthoracic echocardiography did not reveal a cardiac embolic source. Considering the age of the patient, as well as the absence of microfoci on T2*-weighted MRI, cerebral amyloid angiopathy was unlikely. Faurschou et al. recently found an association between GPA and deep vein thrombosis (14). However, sinus thrombosis was not apparent on cerebral angiography in our patient. Since a brain biopsy was not performed, the cause of SMICH was not definitely identified in our case. However, considering the response to corticosteroid treatment, it might well have been CNS vasculitis leading to neuronal dysfunction and SMICH. It should of course be pointed out that our patient's responsiveness to corticosteroids could have been a chance occurrence, since the neurological deficits caused by ICH might have subsided following the disappearance of hematomas. However, cerebral atrophy was noted on brain CT performed a day before the development of SMICH (Fig. 3). Previous case reports have demonstrated the presence of cerebral atrophy in patients with CNS vasculitis (15-18). Taken together, we consider it possible that our patient had CNS vasculitis, which was involved in cerebral atrophy as well as SMICH. It should also

be noted that while ANCA is reported to be a potential marker related to disease activity in GPA (19), the ANCA of our patient was not elevated when she developed SMICH. However, it is arguable that ANCA-positive GPA patients who have been in remission can relapse without the elevation of the ANCA titer (20). It should also be noted that conventional cerebral angiography failed to demonstrate the presence of vasculitis. However, angiography is considered to be less helpful for the evaluation of patients with CNS vasculitis, since the size of the small vessels that are typically affected in GPA is below the resolution of conventional angiography. This is likely to be the reason for the negative cerebral angiography findings in our case.

The pathogenetic mechanisms explaining the simultaneous occurrence of intracranial hemorrhages in SMICH have rarely been described in the literature. In the case of SMICH attributable to the hypertensive rupture of aneurysms, Kabuto et al. hypothesized that the hemodynamic changes caused by the initial hemorrhage could be involved in subsequent hemorrhages in different arterial territories via hemodynamic changes, and that the rarity of SMICH might be explained by counteracting effects, such as reduced cerebral blood flow and increased intracranial pressure (21). Cerebral atrophy was present in our patient prior to the development of SMICH, as described elsewhere, presumably due to brain ischemia mediated by CNS vasculitis. Although cerebral angiography revealed no abnormalities, structural damage of the small vessels, such as the arterioles, capillaries, or venules, might have formed in the affected areas in our patient. Thus, it is possible that persistent and active vascular inflammation might have caused vulnerable small vessels to rupture. Of course, the two intracranial hemorrhages that occurred in our patient might have been coincidental. Further studies to characterize the clinical manifestations of SMICH attributable to CNS vasculitis, especially in terms of underlying brain atrophy, might improve our understanding of the pathogenetic mechanism of SMICH in CNS vasculitis.

Meningeal involvement (pachymeningitis) was another characteristic clinical manifestation found in our patient. Previous studies have demonstrated that patients with GPA and pachymeningitis typically have a limited form of GPA (without pulmonary or renal involvement) and are positive for MPO-ANCA. Although GPA is commonly associated with PR3-ANCA in Western countries (22-25), recent studies, such as RemIT-JAV (Remission Induction Therapy in Japanese patients with ANCA-associated vasculitis), indicate that MPO-ANCA is predominant in Japanese patients with GPA (26). These clinical characteristics were also seen in our case. Although Choi et al. suggested the possible involvement of GPA-related pachymeningitis with subdural hematoma (23), there have been no reports indicating a relationship between ICH and pachymeningitis. It should also be noted that cerebral sinus thrombosis is one of the factors contributing to SMICH (27, 28), and sinus thrombosis is reportedly a complication of pachymeningitis (29). However, sinus thrombosis was not apparent on cerebral angiography

in the present case. It is not known whether our patient had headache and nausea preceding SMICH. However, it is possible that headache and nausea developed in response to pachymeningitis, the disease activity of which increased concomitantly with the CNS vasculitis that caused SMICH; however, this was not confirmed by contrast-enhanced brain MRI.

CNS vasculitis accounts for approximately half of the CNS manifestations of GPA (5). However, ICH due to CNS vasculitis is rare. For example, De Luna et al. investigated 35 patients with GPA and CNS abnormalities and found that pachymeningitis (n=20) was more frequent than cerebral ischemic lesions (n=15) and ICH (n=2) (5). We searched the Medline database and found 24 cases of GPA-associated ICH (including the present case) (3, 4, 30-42). The male to female ratio was 3:1 and the average patient age was 45.1 years. With regard to the pattern of ICH, 14 patients (58%) had ICH (including 1 patient with both ICH and subarachnoid hemorrhage) and the remaining 10 had subarachnoid hemorrhage. A multiple ICH pattern was seen in 6 (43%) of the 14 patients with ICH. Cerebral angiography was performed in 11 patients. However, there were no significant findings in 10 patients, and 1 patient was found to have an aneurysm. The outcome was fatal in 12 (50%) of the 24 patients. The 12 patients who survived were treated with corticosteroids, and 11 of these patients were also treated with cyclophosphamide, suggesting that immunosuppressive therapy should be considered for GPA-related ICH.

In conclusion, patients with GPA may present with ICH, which is considered to be an indication for immunosuppressive therapy, especially if there is a multiple and simultaneous pattern.

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

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