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Recommended Citation
Chen, Yu-Jen; Wong, Ho-Fai; Chen, Chih-Chi; Chen, Chia-Ling; and Chung, Chia-Ying (2015) "Simultaneous Bilateral Intracerebral Hemorrhage in a Case of Wegener’s Granulomatosis: A casereport and Literature reviewarticle," Rehabilitation Practice and Science: Vol. 43: Iss. 4, Article 6.
DOI: 10.6315/2015.43(4)06
Available at: https://rps.researchcommons.org/journal/vol43/iss4/6

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Case Report

Simultaneous Bilateral Intracerebral Hemorrhage in a Case of Wegener’s Granulomatosis: A Case Report and Literature Review

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Background: Simultaneous multiple intracerebral hemorrhages (ICHs) are rare and their underlying mechanisms are unknown. Reported etiologies include hypertension, vasculitis, cerebral amyloid angiopathy, venous sinus thrombosis, coagulopathy, and intracranial vascular anomalies. Granulomatosis with polyangiitis (GPA; Wegener’s granulomatosis) is a necrotizing granulomatous vasculitis affecting small- and medium-sized vessels of the respiratory tract and kidneys. The reported frequency of central nervous system (CNS) involvement in GPA is 0%–16.4%.

Case presentation: A 34-year-old man with hypertension presented with a sudden loss of consciousness and weakness in the right limbs. Brain computed tomography (CT) showed a left basal ganglion hemorrhage and right basal ganglion infarction with hemorrhagic transformation. Brain CT angiography revealed stenosis of the M1 segment of the right middle cerebral artery (MCA) and irregularity of the left MCA branches. GPA was suspected due to persistent sinusitis, microscopic hematuria, detection of cytoplasmic antineutrophil cytoplasmic antibodies, and multiple cerebral vessel irregularities. We assume that the underlying vessel abnormalities resulted from GPA. Uncontrolled hypertension induced the left basal ganglion hemorrhage and right basal ganglion infarction with hemorrhagic transformation. It is known that right M1 territory collateral circulation had been established before this cerebrovascular accident because cerebral angiography revealed complete occlusion of the right M1 segment with profound collateral circulation. Therefore, our patient had intact left side muscle strength despite right basal ganglion infarction with hemorrhagic transformation.

Conclusion: Spontaneous ICH is a rare but fatal complication of GPA. The mechanism underlying simultaneous multiple ICH remains unknown. Considering CNS manifestations can be the first presenting feature of GPA, GPA should be considered in the differential diagnosis of patients with simultaneous multiple ICHs. (Tw J Phys Med Rehabil 2015; 43(4): 263 - 271)

Key Words: Granulomatosis with polyangiitis (Wegener’s granulomatosis), Multiple intracerebral hemorrhages, Vasculitis, Hypertension

INTRODUCTION

Intracerebral hemorrhage (ICH) is the second most common type of stroke, which is one of the leading causes of death worldwide. The reported incidence of ICH is 24.6 per 100,000 person-years.
The reported incidence rate of simultaneous multiple ICHs is 0.9%–4.7%. The mechanism underlying simultaneous multiple ICH remains unknown. Various risk factors have been reported to be associated with the event, including hypertension, vasculitis, cerebral amyloid angiopathy, venous sinus thrombosis, coagulopathy, and intracranial vascular anomalies.

Granulomatosis with polyangiitis (GPA), also known as Wegener’s granulomatosis, is a necrotizing granulomatous vasculitis usually affecting small- and medium-sized vessels of the respiratory tract and kidneys. GPA has the highest incidence rate among all types of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides. The reported frequency of central nervous system (CNS) involvement in GPA varies from 0% to 16.4%.

Here we report the case of a young man admitted due to simultaneous bilateral ICH, which may have resulted from GPA.

**CASE REPORT**

A 34-year-old man with hypertension and no regular medication presented with a sudden loss of consciousness and weakness in his limbs on the right side, which first presented in the morning when he was about to ride his motorbike. He was brought to our emergency department within 1 hour. Looking at his medical history, he reported to being a heavy smoker, smoking in excess of one pack of cigarettes per day for more than 10 years. He also complained of having had a stuffy nose for years, which had not been treated with medication.

Upon arrival at emergency department, his systolic pressure was 222 mmHg and diastolic pressure was 156 mmHg. He rated a 7 on the Glasgow coma scale (GCS) (eye opening: 1, verbal response: 1, motor response: 5). His body weight was 96 kilogram and height was 178 centimeter. His body mass index (BMI) was 30.3. Emergency intubation was performed. Brain computed tomography (CT) revealed a left basal ganglion hemorrhage with a midline shift toward the right. The size of the hematoma on the left side was 53 × 40mm. Hypodensity, mixed with hyperdense strands, was noted in the right basal ganglion with mass effect, favoring cerebral infarction with hemorrhagic transformation. Furthermore, left maxillary sinus opacification was noted, suggestive of sinusitis (Figure 1). Routine urinanalysis revealed a red blood cell (RBC) count of 138/uL without casts. Plain chest X-ray showed bilateral infiltration in the perihilar region. Six hours after losing consciousness, CT angiography showed progression of the hematoma, stenosis of the M1 segment of the right middle cerebral artery (MCA), and irregularity of the left MCA branches (Figure 2). Therefore, an emergency craniotomy was performed to evacuate the left putaminal hematoma. Several coagulated and tangled vessels were noted. He was extubated 1 week after surgery.

The electrocardiogram showed a normal sinus rhythm. Echocardiography revealed impaired left ventricle contractility with global hypokinesis. No thrombus was identified.

The young stroke survey indicated positive cytoplasmic (C)-ANCA, borderline high serum homocysteine (12.7 mg/L), and borderline low serum folate (4.09 ng/mL). Other test results including rheumatoid factor, C3, C4, antinuclear antibodies, renin, aldosterone, 24-h urinary vanillylmandelic acid, and rapid plasma reagin were within normal ranges. Folic acid supplement was prescribed for low serum folate level. Sevikar (Amlodipine 5mg+ Olmesartan 20mg) and atenolol (100mg) were prescribed for blood pressure control. Serum folate and homocysteine levels became normal during follow-up. The combination of nasal inflammation, microscopic hematuria, and C-ANCA detection prompted the diagnosis of GPA on the basis of the American College of Rheumatology criteria (Table 1) and diagnostic criterion in the European Medicines Agency (EMA) algorithm. A positive ANCA in the patient with surrogate markers for GPA allowed the diagnosis of GPA, even without biopsy.

Magnetic resonance angiography was arranged for the intracranial vascular lesion follow-up. It showed complete occlusion of the right MCA and an old hematoma located in the right basal ganglion (Figure 3). Abnormal intracranial vascularity was also noted. We then performed cerebral angiography, and it showed complete occlusion of the right M1 segment and recruitment of the cortical branches from the anterior cerebral artery, temporal artery of the right M1 segment, and right posterior cerebral artery. Some irregularity was noted at
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peripheral branches of the left anterior cerebral artery and MCA. Irregularity, with mild arterial narrowing, was also noted at the lateral segment of the right internal carotid artery. There was no definite cerebral aneurysm or vascular malformation. Due to the significant risk of ICH, a biopsy was not performed (Figure 4). Electromyography and nerve conduction tests showed no evidence of neuropathy in left upper and lower limbs.

The patient’s GCS improved to E4VAM6 (eye opening: 4, verbal response: aphasia, motor response: 6) 1 week after surgery. He was then transferred to a rehabilitation ward. He exhibited dense right hemiplegia with a muscle strength rating of 0/5 and Brunnstrom stage of I in all limbs on the right side. Broca’s aphasia was noted and his Barthel ADL index score was 10 upon admission to rehabilitation ward. Neurehabilitation was arranged. Muscle strength in the limbs on the right side gradually improved. Three months after onset, he could ambulate with moderate assistance under a walker. Language ability also improved, and he exhibited improved verbal expression 4 months after onset. Seven months after onset, his muscle strength improved to 3/5 in the right proximal upper limb and 4/5 in the right proximal lower limb, whereas the right side distal limb muscle strength was 1/5. The Brunnstrom stage of the right proximal upper limb improved to III, and the right distal upper limb improved to II. The Brunnstrom stage of the right lower limb improved to IV. His Barthel ADL index score improved from 10 to 60 after 6 months of inpatient rehabilitation.

DISCUSSION

The majority of spontaneous ICHs are related to hypertension.[18] Although the patient had chronic hypertension, which may have produced hyaline degeneration of the perforating arteries leading to hypertensive ICH,[3] he had possible multiple vasculitis revealed by angiography. It suggested that the patient’s multiple ICHs did not arise from hypertension, but rather may have resulted from underlying GPA.

The mechanisms underlying multiple spontaneous ICHs are not clear. Two possible mechanisms have been proposed. The first is the coincidental rupture of bilateral microaneurysms or perforating arteries. The second mechanism is that the initial ICH results in high blood pressure and hemodynamic change, which causes the second ICH.[18,19] The manifestations of simultaneous multiple hemorrhages depend on the location of the hemorrhages. Symptoms such as motor deficits, sensory deficits, dysarthria, dysphagia, cognitive impairment, and neuropsychological deficits have been reported.[19] Seo et al. found that 43% of patients with simultaneous multiple hemorrhages present with unilateral neurological symptoms, similar to our case.[19] Bilateral simultaneous hemorrhage may lead to marked decreased cerebral flow in bilateral hemispheres. Therefore, multiple ICHs may have worse neurological sequelae compared with single ICH, even if the hemorrhage sizes of the multiple ICH are smaller.[8,18,19]

GPA with CNS involvement is less frequent than that with peripheral nervous system (PNS) involvement. Three mechanisms for CNS involvement in GPA were proposed by Drachman: (1) contiguous spread of granulomatous inflammation from primary sites into CNS; (2) CNS primary granulomatous lesion; (3) vasculitis in the CNS.[20] Multiple microaneurysms are rather specific to vasculitis.[21] Our patient showed vascular irregularity with arterial narrowing observed using angiography. Therefore, CNS vasculitis may have resulted in microaneurysms that are undetectable by cerebral angiography. The microaneurysms then cause the subsequent ICHs in our patient as described in previous study.[22] There have been eight previously reported GPA patients with spontaneous ICH. Subarachnoid hemorrhage was noted in five patients. Multiple ICHs developed in only two patients, and one patient presented with simultaneous unilateral ICH and bilateral SAH (Table 2).[4,20,22-24] Of the six patients in whom ANCA testing was conducted, five patients had positive C-ANCA, whereas one had positive perinuclear (P)-ANCA. Finkielman reported that 92% of GPA patients had positive C-ANCA[25] and that P-ANCA was positive in only 20% of GPA patients. However, at least 10% GPA patients have negative ANCA testing.[26] GPA can involve all systems, similar to other vasculitis. The reported frequency of nervous system involvement in GPA varies from 20% to 58.8%.[12,14,15,27] The incidence rate of PNS involvement is higher than that of CNS involvement. Reported GPA-related PNS involvement ranges from 11% to 44%,[12,15,28,29] whereas the frequency of CNS involvement in GPA varies from 0% to
16.4%. Huang et al. reported the frequency of GPA-related CNS involvement to be 89% (8/9) in a hospital-based study. This high incidence may be attributed to the severity of CNS involvement that requires immediate hospitalization.\(^4\) Yamashita et al. reported a patient with GPA who presented with a headache, nausea, and left-sided numbness. Cerebral angiography revealed cerebral vasculitis.\(^30\) However, the diameter of small vessels, which are frequently affected in GPA, ranges from 50 to 300 \(\mu\)m, which is below the sensitivity of cerebral angiography.\(^13\)

The etiology of our patient’s simultaneous ICH is multifactorial. His smoking habit damaged his vessel walls.\(^31\) The highly suspected GPA made the vessels more vulnerable, as shown by cerebral angiography. We assume that the uncontrolled hypertension may have induced the left basal ganglion hemorrhage and the right basal ganglion infarction with hemorrhagic transformation. In our patient, the right M1 territory collateral circulation had been well established before the accident because cerebral angiography revealed complete occlusion of the right M1 segment with profound collateral circulation. Therefore, our patient may thus have intact left side muscle strength, despite the right basal ganglion infarction with hemorrhagic transformation.

Figure 1. Initial brain CT: (A) Left basal ganglion hemorrhage and right basal ganglion infarction with hemorrhagic transformation. (B) Left maxillary sinus opacification

Figure 2. Follow-up brain CT: left basal ganglion hemorrhage in progression
Simultaneous Bilateral Intracerebral Hemorrhage in Wegener’s Granulomatosis

Figure 3. Brain MRA: (A) Complete occlusion of right middle cerebral artery [arrow]. (B) T2-FLAIR: old hematoma in right basal ganglia and remission of left basal ganglion hematoma. (C) FRFSE T2: left encephalomalacia [arrow].

Figure 4. Cerebral Angiography: (a) Right middle cerebral artery complete occlusion. Irregularity with mild arterial narrowing at lateral segment of right internal carotid artery [arrow] (b) Left internal carotid artery with arterial narrowing [arrow]
Table 1. 1990 criteria for the classification of Wegener's granulomatosis (now known as granulomatosis with polyangiitis)\(^{[16]}\)

<table>
<thead>
<tr>
<th>Nasal or oral inflammation</th>
<th>Development of painful or painless oral ulcers or purulent or bloody nasal discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal chest radiograph</td>
<td>Chest radiograph showing the presence of nodules, fixed infiltrates, or cavities</td>
</tr>
<tr>
<td>Urinary sediment</td>
<td>Microscopic hematuria (&gt;5 red blood cells per high power field) or red cell casts in urine sediment</td>
</tr>
<tr>
<td>Granulomatous inflammation on biopsy</td>
<td>Histologic changes showing granulomatous inflammation within the wall of an artery or in the perivascular or extravascular area (artery or arteriole)</td>
</tr>
</tbody>
</table>

Table 2. GPA patients with spontaneous ICH

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>Sex</th>
<th>ANCA</th>
<th>Respiratory tract</th>
<th>Renal involvement</th>
<th>CNS manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Upper</td>
<td>Lower</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>M</td>
<td>C-ANCA</td>
<td>+</td>
<td>+</td>
<td>Multiple ICH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR3-ANCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>47</td>
<td>M</td>
<td>C-ANCA</td>
<td>-</td>
<td>+</td>
<td>Multiple ICH</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>C-ANCA</td>
<td>+</td>
<td>+</td>
<td>Rt ICH and bilateral SAH</td>
</tr>
<tr>
<td>17</td>
<td>71</td>
<td>M</td>
<td>P-ANCA</td>
<td>-</td>
<td>+</td>
<td>azotemia, nephrotic GN</td>
</tr>
<tr>
<td>18</td>
<td>31</td>
<td>M</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>microhematuria</td>
</tr>
<tr>
<td>19</td>
<td>50</td>
<td>M</td>
<td>C-ANCA</td>
<td>+</td>
<td>+</td>
<td>ARF, crescentic GN</td>
</tr>
<tr>
<td>19</td>
<td>36</td>
<td>M</td>
<td>negative</td>
<td>NA</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
<td>39</td>
<td>M</td>
<td>NA</td>
<td>+</td>
<td>+</td>
<td>NA</td>
</tr>
<tr>
<td>Our patient</td>
<td>34</td>
<td>M</td>
<td>C-ANCA</td>
<td>+</td>
<td>-</td>
<td>microhematuria</td>
</tr>
</tbody>
</table>

GPA= Granulomatosis with polyangiitis
ICH= Intracerebral hemorrhage
CNS= Central nervous system
NA= Not applicable, not specified in text
SDH= Subdural hemorrhage
P-ANCA= Perinuclear anti-neutrophil cytoplasmic antibodies
C-ANCA= Cytoplasmic anti-neutrophil cytoplasmic antibodies
PR3-ANCA= Proteinase 3 anti-neutrophil cytoplasmic antibodies
SAH= Subarachnoid hemorrhage

CONCLUSION

In summary, spontaneous ICH is a rare but fatal complication of GPA.\(^{[20]}\) We report a patient with highly suspected GPA presenting with bilateral basal ganglion hemorrhage. Unlike most of the reported patients with bilateral ICH, our patient recovered well. We assume that the profound cerebral collateral circulation established before the cerebrovascular accident may be accountable for his relatively favorable outcome. Considering CNS manifestation can be the first presenting feature of GPA, GPA should be considered in the differential diagnosis for patients with multiple spontaneous ICH.

REFERENCES
Simultaneous Bilateral Intracerebral Hemorrhage in Wegener’s Granulomatosis


韋格納肉芽腫病人併雙側同時顱內出血：個案報告及文獻回顧

陳渝仁 1 黃浩輝 2,3 陳芝琪 1,4 陳嘉玲 1,4,5 鍾佳英 1,4

長庚紀念醫院復健科 1 林口長庚醫院影像診療部 2 長庚大學醫學院醫學影像暨放射科學系 3
長庚大學醫學院 4 長庚大學早期療育研究所 5

同時顱內多處出血在臨床上罕見且造成的病理機制未明，可能原因包括高血壓、血管炎、腦澱粉樣血管病、靜脈竇血栓、凝血功能異常及顱內血管畸形。

韋格納肉芽腫為主要影響呼吸道及腎臟的中小型血管的壞死性肉芽腫性血管炎，文獻指出韋格納肉芽腫會影響到中樞神經系統的發生率為0%到16.4%。

本個案報告病患為34歲男性，本身有高血壓但未規律服藥控制。病患的初始表現為突然意識喪失及右側肢體無力，腦部電腦斷層顯示左側基底核出血及右側基底核梗塞併出血性轉化，腦部電腦斷層血管攝影顯示右側中大腦動脈M1分支阻塞及左側中大腦動脈血管型態異常，由於多處顱內血管異常，加上鼻竇炎、顯微性血尿及抗嗜中性白血球細胞質抗體(c-ANCA)陽性，因此病人診斷被懷疑是韋格納肉芽腫。

我們推論顱內血管異常源自於韋格納肉芽腫，突發的高血壓造成左側基底核出血及右側基底核梗塞併出血性轉化，血管攝影顯示右側中大腦動脈M1分支阻塞但是已經建立側支循環，因此臨床上病人的左側肢體在發病後保有完整的肌力。

自發性顱內出血是韋格納肉芽腫少見但嚴重的併發症，造成顱內多發性出血的明確生理機轉未明，由於中樞神經的表現有可能是韋格納肉芽腫症的第一個表現症狀，因此在同時顱內多處出血的情況下，韋格納肉芽腫須列入為臨床上可能的鑑別診斷。（台灣復健醫誌2015；43(4):263 - 271）

關鍵詞：韋格納肉芽腫(Granulomatosis with polyangiitis (Wegener’s granulomatosis))，多發性顱內出血 (Multiple intracerebral hemorrhages)，血管炎(Vasculitis)，高血壓(Hypertension)

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