Extremely rare complication of granulomatosis with polyangiitis. Aneurysmal subarachnoid haemorrhage

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ABSTRACT
The systemic vasculitis of the small-medium arteries, arterioles, venules and rarely large arteries that involves respiratory system and kidneys was defined as Granulomatosis with Polyangiitis (GPA) disease by Wegener in 1936. Intracranial aneurysms and subarachnoid haemorrhage (SAH) are extremely rare complications of GPA and our case will be the 2nd case treated with clipping aneurysm and the 11th case with subarachnoid haemorrhage in the literature.

A 43-year-old man presented to the emergency room with a severe headache and was admitted for further evaluation. He had GPA diagnosis 14 years ago with cytoplasmic anti-neutrophil cytoplasmic antibody (C-ANCA) and PR3-ANCA positive laboratory tests and kidney biopsy. SAH was seen on cranial computed tomography (CT) images. Then cerebral digital subtraction angiography (DSA) performed and right middle cerebral artery aneurysm exposed. Aneurysm was clipped without any complication. Intracranial aneurysms and SAH are extremely rare complications of GPA. GPA related aneurysmal SAH is an exceptional condition in neurovascular pathology. Monitoring patients with GPA for SAH must be remembered and kept in mind as a diagnosis.

INTRODUCTION
The systemic vasculitis of the small-medium arteries, arterioles, venules and rarely large arteries that involves respiratory system and kidneys was defined as Granulomatosis with Polyangiitis (GPA) disease by Wegener in 1936 (1). Wegener defined the disease with the findings that includes focal necrotizing glomerulonephritis, respiratory tracts'...
necrotizing granulomatous vasculitis and systemic vasculitis as a diagnostic triad (1).

Inflammatory and autoimmune mechanisms are discussed for the pathogenesis of GPA but it still remains controversial. The involvement of central nervous system (CNS) has been reported in 7-11% whereas the cases with aneurysmal subarachnoid hemorrhage (SAH) are excepted (2). Clinical symptoms with positive proteinase 3 (PR-3) anti-neutrophil cytoplasmic antibody (ANCA) laboratory test shows both high sensitivity and specificity in diagnosis of GPA.

Intracranial aneurysms and subarachnoid hemorrhage are extremely rare complications of GPA. Previously, only 10 cases of SAH related to GPA have been reported in the literature. Only 1 of them was treated with surgical aneurysm clipping.

**CASE REPORT**

A 43 year old man presented to the emergency room with a severe headache. No pathological findings were detected in the neurological examination. He had no history of hypertension or a cardiac disease. Cranial computed tomography (CT) was performed and the patient was diagnosed with subarachnoid hemorrhage (Figure 1A). While the patient was preparing for cerebral digital subtraction angiography (DSA), his neurological examination suddenly worsened. The patient was intubated and cranial CT performed again (Figure 1B). Cerebral DSA was performed to the patient who had bleeding again and right middle cerebral artery aneurysm exposed (Figure 1C, D).

It was learned that the patient was followed up with the diagnosis of GPA. He applied to hospital with the symptoms of fever, coughing and hemoptysis in 2003. In his examination, bilateral arthritis on lower extremities, palpable purpura, episcleritis in the eyes were present. In thorax CT, consolidation areas and 10 cm cavitation were detected in the right lung. Urine test showed proteinuria and kidney biopsy reported as GPA. Laboratory tests revealed cytoplasmic anti-neutrophil cytoplasmic antibody (c-ANCA) and PR3-ANCA positivity. As a result of all tests, steroid and cyclophosphamide treatment was given to the patient.

In 2015, the patient had a tonic-clonic seizure in the bathroom and was found unconscious. He had homonim hemianopsia, left facial paralysis and hemiparesia. There was no hemorrhage on cranial CT. The diffusion weighted magnetic resonance imaging (DW-MRI) showed an acute ischemia in the right temporal-occipital and frontobasal areas. MRI-Angiography had been found normal.

**FIGURE 1** - A. Preoperative cranial CT image showing SAH; B. Intracerebral hemorrhage is seen after re-bleeding; C-D. Preoperative DSA images showing right middle cerebral artery aneurysm.

**FIGURE 2** - A-B. Cranial CT axial sections in the early and late postoperative periods; C-D. Postoperative DSA images showing severe vasospasm and right middle cerebral artery aneurysm clipped without remnant.
Decompressive craniectomy was performed and right middle cerebral artery aneurysm was clipped without any complication. External ventricular drainage was placed due to hydrocephalus. Cranial CT was performed in the early and late postoperative periods (Figure 2A, B). Postoperative DSA was performed to the patient. The aneurysm was clipped without remnant, but serious vasospasm was observed (Figure 2C, D). Chest X-ray and thorax CT showed noduler infiltrations (Figure 3A, B). The patient died on the 26th postoperative day due to respiratory tract infection and severe vasospasm.

**FIGURE 3** - A. X-ray chest graphy and; B. Thorax CT axial section showing noduler infiltrations in medial region.

**DISCUSSION**

GPA is typically diagnosed with by activated neutrophils accumulations, vasculitis, formation of microabscess, granulomas, glomerulonephritis and necrosis in pathological examination (3). Wegener defined the disease with the findings that includes focal necrotizing glomerulonephritis, respiratory tracts' necrotizing granulomatous vasculitis and systemic vasculitis as a diagnostic triad (1).

In 1990, The American College of Rheumatology announced diagnostic criterias to classify GPA (4). Classical diagnostic criterias were an abnormal sediment of urine, abnormal findings like cavities, nodules and infiltrations on a chest radiograph, oral or nasal mucosal ulcers; and biopsy concluded with granulomatous inflammation. Minimum two of the four criterias requested for the diagnosis of GPA and hemoptysis is added to the traditional format so classification tree was defined (4). Classification tree was reported more specific and sensitive than the traditional format (4).

Neurologic involvement is rarely seen in GPA and reported as ranging from 22% to 54% in the literature (5). Drachman et al. have discussed three major mechanisms which could be summarized as vasculitis of CNS, intracranial granuloma and extracranial granuloma invasions on causes of CNS involvement in GPA (6). Seror et al. reported CNS involvement of GPA with six patients that three of them with pituitary involvement, two patients with pachymeningitis, and last patient with cerebral vasculitis (7). The CNS involvements were attributed to GPA because they were diagnosed at disease onset or flare and also extracranial involvements, other CNS disease etiologies had been excluded, and/or they had attributed to sustained immunosuppressive therapy.

CNS vasculitis was reported as the cause of intracranial hemorrhages, transient ischemic strokes, cerebral infarctions, venous or arterial thrombosis, encephalopathy, ischemic myelopathy, seizures, dementia, altered consciousness, cortical blindness, visual loss and cognitive impairment (3, 8-11). Because of the rarity of CNS involvements in GPA, no specific treatment suggestions exist for management of them except combining cyclophosphamide and corticosteroids as systemic GPA therapy (12, 13).

Subarachnoid hemorrhage in GPA has been rarely reported in the literature (Table 1) (2, 6, 8, 14-19). Only two cases presented with subarachnoid hemorrhage and exposed the aneurysms with cerebral angiography. Takei et al. confirmed an anterior choroid artery aneurysm and Marnet et al.
reported an anterior communicating artery aneurysm (2, 16). Our case is 3rd as the middle cerebral artery aneurysm. Takei et al. had clipped the aneurysm as a first case, but Marnet et al. could not have clipped the aneurysm because of a vasculitis flare-up of disease (2, 16). So our case is the 2nd case of subarachnoid hemorrhage treated by clipping the aneurysm. Onodera et al. reported an incidentally found carotis aneurysm without subarachnoid hemorrhage in GPA but they made balloon occlusion with endovascular procedure for treatment (5). Survival rate is very low for the aneurysms of GPA but we can not evaluate the reason of it because the information about patients is limited due to fast deterioration (Table 1).

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<td>Drachman et al. (6)</td>
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<td>Chronic rhinitis, persistent skin ulcers</td>
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<td>Venning et al. (15)</td>
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<td>Fomin et al. (18)</td>
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<td>Marnet et al. (2)</td>
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<td>Subarachnoid hemorrhage</td>
<td>Cerebral angiography: Aneurysm</td>
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**Table 1.** Cases of subarachnoid hemorrhage with GPA in the literature
Takei et al. reported the possible mechanism for the aneurysmal bleeding with GPA may have involved the ANCA-cytokine sequence, with activated polymorphonuclear neutrophils adhering to the endothel of the aneurysm origin, and with polymorphonuclear neutrophils degranulation liberating PR-3 and human leukocyte elastase (HLE) (16). Then PR-3 caused apoptosis of arterial smooth muscle cells. The destruction of the internal elastic lamina may also attributed to aneurysm formation and rupture (16).

CONCLUSION

Intracranial aneurysms and subarachnoid hemorrhage are extremely rare complications of GPA. GPA related aneurysmal SAH is an exceptional condition in neurovascular pathology. As inflammatory mechanisms are involved in the pathogenesis of aneurysm, the vasculitis flare-up could account for this SAH. Surgical clipping of aneurysm could be done for the treatment of aneurysmal subarachnoid hemorrhage in GPA patients. Finally, monitoring patients with GPA for SAH must be remembered and kept in mind as a diagnosis.

REFERENCES