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【 CASE REPORT 】

Multiple Cerebral Infarctions Accompanied by Subcortical and Subarachnoid Hemorrhaging in Bilateral Border Zone Areas in a Patient with Eosinophilic Granulomatosis with Polyangiitis

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Abstract:
Eosinophilic granulomatosis with polyangiitis (EGPA) is often associated with peripheral neuropathy, but reports of central nervous system involvement are quite rare. We herein report a patient with EGPA first identified as having hypereosinophilia who later developed asthma, eosinophilic otitis media, sinusitis, and hemorrhagic colitis. She subsequently developed hemiparesis. Head magnetic resonance imaging revealed multiple cerebral infarctions with subcortical and subarachnoid hemorrhaging colocalized at the bilateral border zone areas. She was diagnosed with EGPA-induced stroke and successfully treated with oral prednisolone. Inflammation in the small cerebral arteries in EGPA may induce bilateral border zone infarction with colocalizing subcortical and subarachnoid hemorrhaging.

Key words: border zone infarction, subarachnoid hemorrhaging, subcortical hemorrhaging, eosinophilic granulomatosis with polyangiitis, EGPA, prednisolone

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Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA) is often associated with peripheral neuropathy in the form of mononeuritis multiplex, but reports on central nervous system involvement are quite rare (1-3). Neurologic involvement was reported in 55% of cases in a large series, including peripheral neuropathy in 51%, whereas central nervous system (CNS) and cranial nerve involvements were reported in just 5% and 3%, respectively (4). In the largest review of the literature, in addition to original cases, which included 88 cases of EGPA with central nervous system involvement, André et al. reported 46 cases (52%) of cerebral infarction and 21 cases (24%) of intracerebral hemorrhaging and/or subarachnoid hemorrhaging (3).

We herein report a patient with EGPA who suffered from multiple cerebral infarctions with asymptomatic subcortical and subarachnoid hemorrhaging observed concomitantly. Inflammation in the small cerebral arteries in EGPA may induce bilateral border zone infarctions with colocalizing subcortical and subarachnoid hemorrhaging.

Case Report

A 69-year-old Japanese woman suddenly noticed left-hand weakness while performing household tasks. She later became unsteady on a bicycle and noticed left shoulder pain and purpura a few centimeters in diameter on all extremities. She was referred to our hospital by a nearby clinic.

Previously, hypereosinophilia had been identified at a medical checkup at 40 years old. She had developed asthma at 43 years old and been treated with low-dose betamethasone until the present admission. She had eosinophilic otitis media and sinusitis at 46 years old. She had also developed hematochezia at 63 years old. At that time, she had been diagnosed with ulcerative colitis and began taking prednisolone and mesalamine. She experienced transient myalgia and

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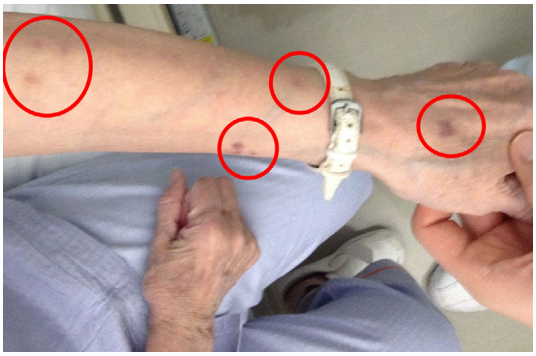

Figure 1. Disseminated purpura on the left upper extremity. A biopsy revealed simple purpura without eosinophilic infiltration.

arthralgia that disappeared before a closer examination could be performed. She also had complaints of pleuritis at 66 years old. She had no family history of neurological diseases or collagen disorders. Her only allergic disease was pollinosis. She was a teacher at a nursing school.

On admission, her height was 147 cm, and her weight was 52 kg. Her blood pressure was 120/88 mmHg, and her pulse was 75/min and regular. Body temperature was 35.9 ℃. A physical examination revealed no rales in the lungs and no cardiac murmur. No lymph nodes were palpable. She had purpura a few centimeters in diameter in all extremities (Fig. 1).

On a neurological examination, she was right-handed. She was conscious and alert, and her vision was normal, although her pupils were isochoric with brisk reaction to light. Extraocular movement was normal. Neither facial nor bulbar palsy was observed. Neither dysarthria nor dysphagia was noticed. The Barré sign of the left upper extremity was positive with pronation. The Mingazzini sign of the left lower extremity was positive. Muscle strength on the manual motor test was 5/5$^-$ in the deltoid, biceps, triceps, wrist extensor, wrist flexor, iliopsoas, quadriceps, hamstrings, tibialis anterior, and gastrocnemius. Deep tendon reflexes were all normal. Pathological reflexes, including Hoffmann, Trömner, Babinski, and Chaddock, were all negative. Sensory stimulation of light touch, pain, and temperature on the back of the left lower extremity induced unusual feelings, as if they were being touched through a veil, although the sensation had been noted since a prior lumbar injury. The position and vibration sense was normal. Coordination tests, including the finger-nose-finger test, pronation/supination test, and heel-to-shin test, were all clumsy on the left to a degree corresponding to the weakness. The station was stable, but standing with one foot was unstable on the left. Romberg's sign was negative. An unstable wide-based gait was noticed. Tandem gait was impossible. Her National Institute of Health Stroke Scale (NIHSS) score was 3.

Laboratory tests showed white blood cell count of 6,200/μL and eosinophil rate of 30%. Erythrocyte sedimentation rate was 36 mm/h. No abnormalities were found in the coagulation system, including FDP and D-dimer. Total IgE was 440 IU/mL, IgG 1,762 mg/dL and IgG4 306 mg/dL. Anti-nuclear antibodies were negative, and proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA) and myeloperoxidase (MPO)-ANCA were within the normal range. No increase in creatine kinase, brain natriuretic peptide, or troponin T was found. Her cerebrospinal fluid was clear and colorless. The cell count was 2/μL (mono 100%), and the total protein was 31 mg/dL.

Diffusion-weighted brain magnetic resonance imaging (MRI) revealed spotty, high-intensity lesions mostly localized at the bilateral border zones, suggesting acute small infarctions (Fig. 2A). T2-weighted imaging showed high-intensity lesions wider than those on diffusion-weighted imaging (DWI), indicating a mixture of acute and subacute infarctions (Fig. 2B). T2*-weighted images revealed tiny cortical and subcortical hemorrhaging close to the infarcts as well as small subarachnoid hemorrhaging (Fig. 2C). No abnormality was found in the major cerebra arteries on MR angiography (Fig. 2D). Susceptibility-weighted images obtained two months later more clearly delineated low-intensity spots in the cortex, subcortex, and subarachnoid spaces (Fig. 2E). No additional infarcts were detected on DWI or T2-weighted imaging two months later.

A conventional 12-lead electrocardiogram repeatedly performed during hospitalization showed no abnormalities. Holter electrocardiographic monitoring revealed no arrhythmia. Transthoracic echocardiography showed neither intracardiac thrombus nor patent foramen ovale. Cardiac MRI was not performed. No significant plaque was found by carotid echo. Results of nerve conduction studies on the left median, ulner, tibial, and sural nerves were all within normal limits.

A skin biopsy of the purpura on the left forearm revealed superficial perivascular dermatitis without findings of eosinophilic infiltration or vasculitis, suggesting simple purpura. Colonoscopy revealed eosinophilic infiltration without findings of vasculitis, suggesting eosinophilic colitis (Fig. 3).

Based on the clinical history of asthma followed by vasculitic diseases with eosinophilia and elevated IgE, she was diagnosed with EGPA-induced stroke.

Before admission to the hospital, she had been treated with apixaban for possible cardioembolic stroke, and oral betamethasone 0.25 mg/kg had been prescribed for skin lesions at the nearby clinic. Based on the diagnosis of EGPA-induced stroke, apixaban was terminated, and she was treated with oral prednisolone 0.5 mg/kg (Fig. 4). Her neurological symptoms, including left hemiparesis and unstable gait, gradually improved with normalization of eosinophilia. As of one year after discharge, she had had no recurrence of stroke, including asymptomatic ischemic lesions on MRI, with low-dose prednisolone.

Discussion

In the 2012 Revised International Chapel Hill Consensus

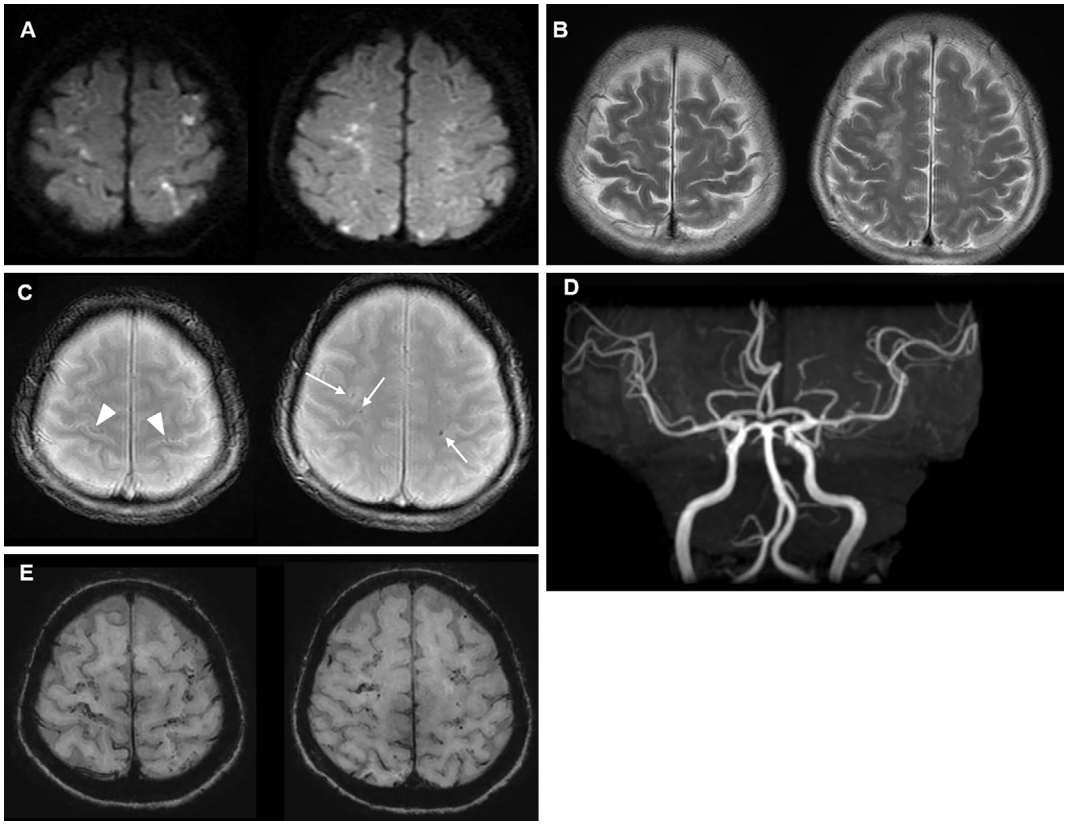

Figure 2. **Head MRI was taken at a local clinic when the initial symptoms developed. Diffusion-weighted images (A) and T2-weighted images (B) show spotty high-intensity lesions localized at the bilateral border zone areas. Some of the cortical and subcortical lesions at the border zone (arrow) and some subarachnoid lesions (arrowhead) showed a low intensity on T2*-weighted images, suggesting microhemorrhaging (C). MR angiography revealed no stenosis in the large cerebral arteries (D). Two months later, low-intensity spots on susceptibility-weighted images were increased in the cortex, subcortex and subarachnoid spaces (E).**

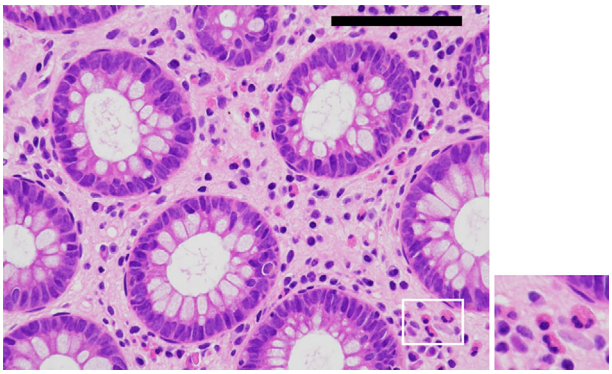

Figure 3. **A biopsy of the colon revealed eosinophilic infiltration, compatible with eosinophilic colitis, although findings of vasculitis were not noted. Hematoxylin and Eosin staining. Scale bar 100 μm. The magnified image on the right clearly illustrates eosinophilic infiltration.**

Conference Nomenclature of Vasculitides, EGPA was defined as eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels and associated with asthma and eosinophilia (5). In the present case, hypereosinophilia and asthma preceded vasculitis-related symptoms, including eosinophilic colitis, transient arthralgia and myalgia and purpura with stroke, fulfilling the classical criteria of EGPA even without biopsy findings of vasculitis (6).

EGPA may often be associated with peripheral neuropathy, but central nervous system involvement is quite rare. In the largest review of the literature, André et al. reported 46 cases of cerebral infarction, 9 cases of intracerebral hemorrhaging, and 12 cases of subarachnoid hemorrhaging among 88 cases of EGPA with central nervous system involvement between 1992 and 2014 (3). Yamada et al. reported a case of EGPA with massive subcortical hemorrhaging in the parietal lobe accompanied by multiple lesions of subarachnoid hemorrhaging and small infarction colocalized in the border zone area (7). She additionally reviewed 7 cases of subcortical hemorrhaging with EGPA, although none of them presented with both cerebral infarction and subarachnoid hemorrhaging concomitantly (7). The present case is the first to show that cerebral infarction can colocalize with subcortical hemorrhaging and subarachnoid hemorrhaging in the border zone area. Until recently, T2*-weighted and susceptibility-weighted imaging have not been routinely performed in

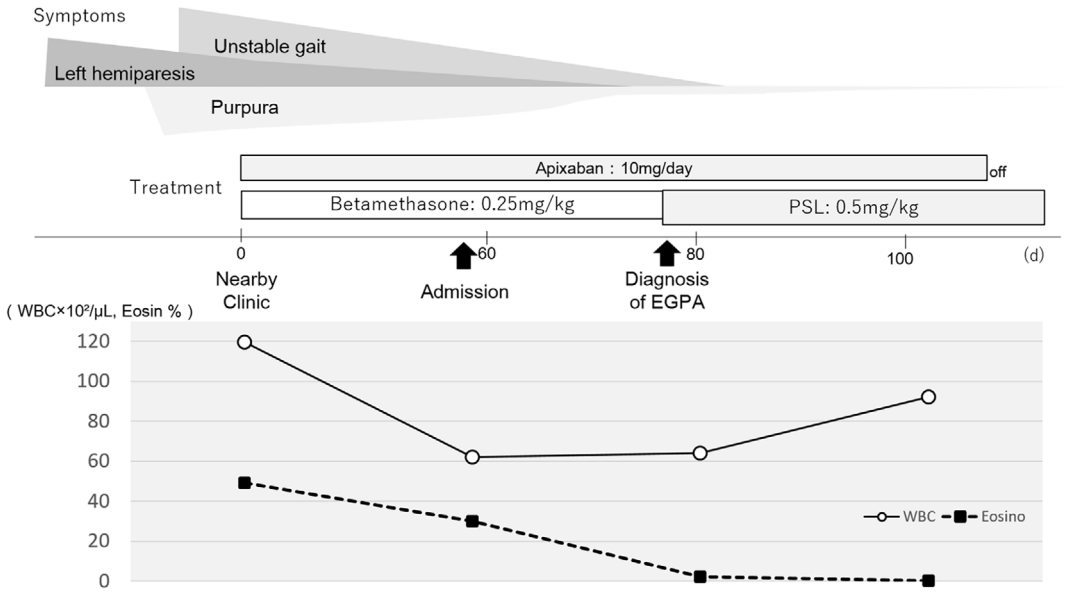

Figure 4. Clinical course of the present case showing that the symptoms and laboratory data findings improved after treatment with betamethasone and disappeared completely after prednisolone (PSL) treatment.

cases where ischemic stroke was suspected. This might have resulted in such detailed disease progression being overlooked in previous cases. In the present case, anticoagulant was started at a local clinic. However, its influence on the hemorrhagic changes may have been negligible, as such agents usually cause large and symptomatic hemorrhaging once the hemorrhagic process is started.

Ischemic lesions are the most frequent findings of CNS manifestations in EGPA, representing half of cases with CNS involvement (3). Such lesions may be small and numerous, being distributed along bilateral border zone areas, including cortical and subcortical areas, as in the present case. The border zone area is characterized by a low hydrostatic pressure, and its microcirculation may easily be affected by hypereosinophilia and vasculitis. In the present case, ischemic lesions were accompanied by subcortical and subarachnoid hemorrhaging, suggesting that vasculitis can make the vessel wall vulnerable while disturbing the peripheral flow in the same lesion. The initial occurrence of cerebral infarcts and the apparently delayed detection of microhemorrhaging and subarachnoid hemorrhaging suggest that disruption of the vessel wall may follow the initial disturbance of microcirculation.

In contrast, cardioembolism has been reported in EGPA-induced stroke, especially in cases where the coronary artery is involved in vasculitis (8). EGPA-induced cardioembolism can present as a large cortical infarction or large infarction in the basal ganglia, in contrast to the multiple spotty infarctions seen in the bilateral border zone observed in the present report. A detailed evaluation of the heart revealed no abnormality in the present case.

As in EGPA, endocarditis and eosinophilic cardiomyositis is also reported in hypereosinophilic syndrome, a closely related disease to EGPA (9, 10). Cardioembolism was claimed as a mechanism underlying infarction in the border zone area in some cases (9, 10), although local thrombus formation and hyperviscosity might have been solely or additionally involved in others (10, 11). In addition, further MRI evaluations with hemorrhaging-sensitive conditions may reveal vascular lesions in such cases.

Prednisolone was effective in treating ischemic lesions and purpura as well as suppressing recurrence of stroke in the present case. The number of eosinophils, an indicator of treatment control, was well controlled by prednisolone. Treatment with classical immunosuppressants and recently developed mepolizumab may also be useful in refractory cases (12). In the present case, a direct oral anticoagulant was first used for possible cardioembolism. Given the risk of subcortical and subarachnoid hemorrhaging, antithrombotic drugs should not be administered in cases of EGPA-induced cerebral infarction. In the present case, the CNS lesions were all small and mostly asymptomatic. The EGPA activity was easily suppressed with prednisolone. The kidney was not involved in the present case. Taken together, these factors contributed to the good prognosis of our patient.

In conclusion, we encountered a case of EGPA-induced multiple cerebral infarction accompanied by asymptomatic subcortical and subarachnoid hemorrhaging in the same border zone area. Hypereosinophilia and inflammation in the small cerebral arteries may have induced microcirculatory disturbance with vessel wall injury.

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

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