Multiple Cerebral and Cerebellar Infarcts as the First Clinical Manifestation in a Patient with Churg-Strauss Syndrome: Case Report and Literature Review

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Abstract-

Purpose: Churg-Strauss syndrome (CSS) is a rare autoimmune disease with small-vessel vasculitis. Neurological manifestation of CSS is common. Central nervous system is less frequently involved than that of peripheral nervous system.

Case Report: We report a case of 60-year-old man who presented with acute onset of right hemiparesis and impaired cognition. The presence of hypereosinophilia, asthma, sinusitis and extravascular eosinophil accumulation led to the diagnosis of Churg-Strauss syndrome. Brain magnetic resonance imaging (MRI) revealed multiple infarcts in bilateral cerebral and cerebellar hemispheres. The neurophysiology study did not reveal peripheral neuropathy. The patient was effectively treated with methylprednisolone, cyclophosphamide and warfarin.

Conclusion: Symptoms and signs of central nervous system can be the initial neurological manifestation of CSS patients. CSS should be considered while patients have stroke and hypereosinophilia. In our patient, there is a good response to timely steroid, immunosuppressant and anticoagulant therapies.

Key Words: Churg-Strauss syndrome, allergic granulomatosis and angiitis, ANCA-associated vasculitides, cerebral and cerebellar infarctions

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INTRODUCTION

Churg-Strauss syndrome, also called allergic granulomatosis and angiitis, is a rare immune disorder with small-vessel vasculitis. Six criteria of American College of Rheumatology (ACR) [(1)] are asthma, eosinophilia, neuropathy, pulmonary opacities, paranasal sinus abnormality and extravascular eosinophil accumulation - more than four of these are necessary to confirm the diagnosis. There is also involvement of dermatologic, cardiovascular, gastrointestinal, respiratory, nephrological and nervous systems. Corticosteroid therapy is the classic and effective regimen. Several alternative treatments were also proposed. Peripheral neuropathy is a

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common neurological manifestation. Ischemic stroke is a relatively unusual finding.

CASE REPORT

This 60-year-old man, having asthma for ten years, allergic rhinitis with sinusitis for six years, was admitted to our hospital for acute onset of right hemiparesis (medical research council [MRC] grading for muscle power: 3) and disorientation. Tendon reflex grading was symmetrically 2+ in four limbs. Physical examination showed skin purpura over trunk and limbs (Figure 1), bilateral coarse breathing sound and mild fever (body temperature: 37.6˚C). Blood pressure, pulse rate and respiratory rate were within normal range. Chest X-ray revealed bilateral pulmonary infiltrates.

Electrocardiography (ECG) showed normal sinus rhythm, left ventricular hypertrophy and ischemic change of anterior-lateral wall (inverted T wave in leads of aVL and V3-V6) without ST-T elevation. With elevated cardiac enzymes (TnI＝35.53 ng/mL, CK＝329 IU/L, CKMB＝17 ng/mL), non-ST elevation acute myocardial infarction was suspected. Yet coronary angiography revealed no stenosis. 24-hr Holter ECG revealed no atrial fibrillation. Cardiac echo showed endomyocardial fibrosis in left ventricle (Figure 2). Ejection fraction of left ventricle was 64%. Right ventricular endocardium biopsy revealed eosinophilic and lymphocytic infiltration (Figure 4). Extracranial carotid duplex sonography disclosed mild atherosclerosis of right external carotid artery and left internal carotid artery.

Peripheral blood examinations disclosed leukocytosis with hypereosinophilia (WBC: 21370 /μL; eosinophil: 64%; total eosinophil count: 13676 /μL). Prothrombin time (PT) was 14.2 seconds (international normalized ratio=1.57). Activated partial thromboplastin time was 27.9 seconds. We did not check D-dimer and fibrinogen. There were also elevated CRP (8.33 mg/dL) and ESR (1hr: 83 mm; 2hrs: 116 mm), increased IgE (352 kU/L), positive antinuclear antibodies (ANA) and perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA). HbA1C was 6.5 and lipid profile was within normal range (Cholesterol=164 mg/dL, Triglyceride= 87mg/dL, LDL-C=100mg/dL, HDL-C=61mg/dL). Other inflammatory markers including RA factor, cytoplasmic anti-neutrophil cytoplasmic antibodies (c-ANCA) and anti-phospholipid antibodies were negative, as were tumor markers (CEA, CA199, AFP, SCC and PSA).

There were several old brain insults in bilateral subcortical cerebral region in brain computed tomography. Brain MRI showed multiple small acute ischemic lesions, subcortically and cortically, in bilateral cerebral

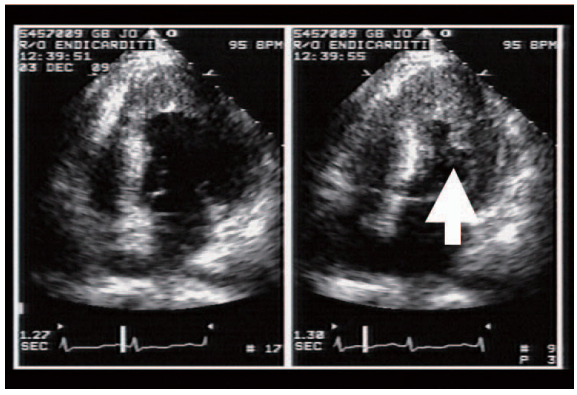

Figure 2: Echocardiography showed endomyocardial fibrosis in left ventricle (white arrows).

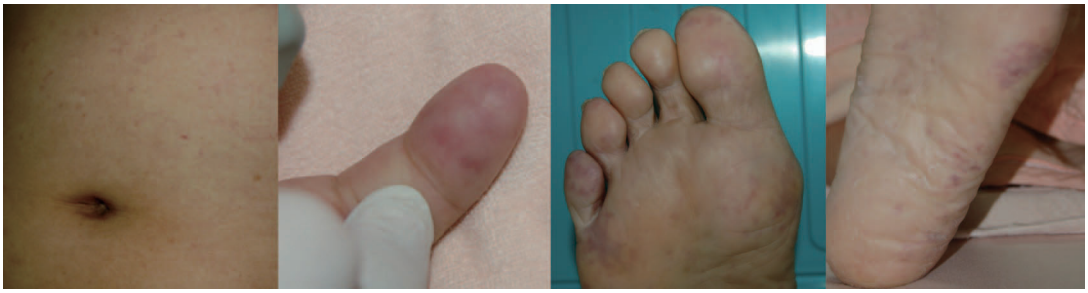

Figure 1: Multiple purpura of trunk and bilateral limbs.

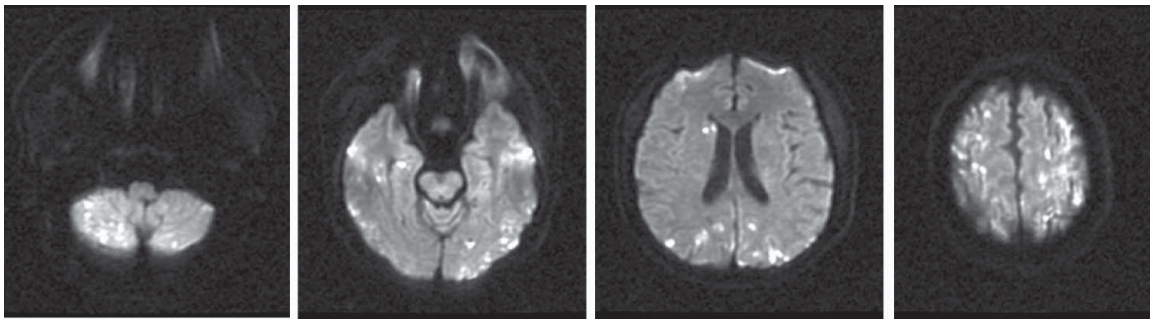

Figure 3: Diffusion-weighted magnetic resonance imaging revealed multiple infarcts of bilateral cerebral and cerebellar hemispheres, cortically and subcortically.

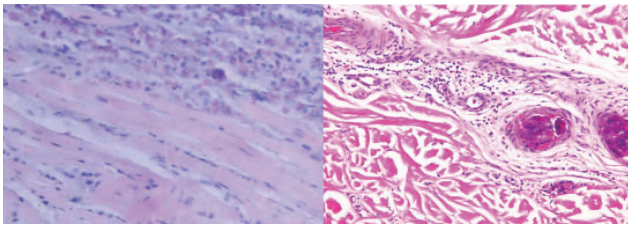

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Figure 4: Left picture: right ventricular endocardium biopsy revealed eosinophilic and lymphocytic infiltration. Right picture: Skin biopsy of right sole revealed vascular occlusion and extravascular infiltration with eosinophil.

and cerebellar hemispheres (Figure 3). There was no evidence of peripheral neuropathy in motor, sensory nerve conduction studies and F-wave. Skin biopsy of right sole revealed vascular occlusion and extravascular infiltration with eosinophil (Figure 4). Fecal exam showed negative parasite finding. There was no pathogen growth in blood bacterial culture.

The presence of these findings led to the diagnosis of Churg-Strauss syndrome by ACR criteria. The patient was treated with intravenously methylprednisolone 40mg daily for 5 days and then we shifted it to orally prednisolone 30mg and cyclophosphamide 50mg daily. Treatment with corticosteroid and cyclophosphamide alleviated clinical deterioration. Anticoagulant therapy (warfarin 2.5mg daily) was added for prevention of thromboembolism formation. At discharge, oral prednisolone, cyclophosphamide and warfarin were kept. Muscle strength of right limbs were improved (MRC grading: 4). Follow-up ESR and total eosinophil count four months later remained in normal range (ESR: 1hr: 8mm; 2hrs: 20mm; total eosinophil count: 50 /μL).

DISCUSSION

Churg-Strauss syndrome is defined as one of the ANCA-associated vasculitides. Sinico et al.[2] reported about 38% of CSS patients present positive ANCA. Most ANCA-positive in CSS patients is related to a perinuclear IgG immuno-staining pattern targeting to myeloperoxidase. ANCA-positive patients have increased frequency of purpura, renal and nervous system involvement. Cardiac manifestation is more frequent in ANCA-negative patients[2].

Neurological manifestation of CSS is common (62-86%)[3]. Peripheral nervous system (PNS) is often affected (53-78%), predominantly mononeuritis multiplex[3]. Involvement of central nervous system (CNS) is less frequent (6-39%)[3].We listed all available studies searched from PudMed database in Table 1 [3-30,34,35] classified in four parts (subarachnoid hemorrhage, intracerebral hemorrhage, cerebral/cerebellar infarct or gliosis and spinal cord lesion). In the serial cases of subarachnoid hemorrhage, we found a tendency of middle-aged female predominance. Intracerebral hemorrhage is seen more in young and middle-aged male adults. Ghaeni et al. reported a 77-year-old CSS woman had similar clinical findings as those in our case (Table 2)[34], except endomyocardial fibrosis. There were no global aphasia and respiratory failure in our patient.

Table 1. Reports of CNS manifestation in CSS Patients

CNS manifestation	Reports	Age/Gender	CNS manifestation	Reports	Age/Gender
Subarachnoid	Menditto et al. 2012[4]	64/F	Cerebral /Cerebellar	Tanaka et al. 2011[35]	77/F
hemorrhage (SAH)	Shimizu et al. 2011[5]	60/F	infarct or gliosis	Kumar et al. 2011[19]*	13/M
	Sheerin et al. 2008[6]	37/F		Sairanen et al. 2011[20]	49/M
	Sakamoto et al. 2005[7]	36/F		Sacco et al. 2011[21]*	n.k./n.k.
	Tyvaert et al. 2004(+ICH)[8]	47/F		Wolf et al. 2010[3]	61/M, 67/M, 45/F
	Calvo-Romero et al. 2002[9]	47/F		Twardowsky et al. 2010[22]	7/M
	Chang et al. 1993(+IVH)[10]	47/n.k.		Ghaeni et al. 2010[34]	77/F
Intracerebral	Halliday et al. 2012[11]	43/M		Bhagirath et al. 2008[23]	30/M
hemorrhage (ICH)	Mencacci et al. 2011[12]	29/M		Kang et al. 2001[24]*	n.k./n.k.
	Mishra et al. 2007	45/M		Dinc et al. 2000[25]	46/F
	(+IVH&SAH)[13]			Aoshima et al. 1998[26]*	23/F
	Winek et al. 2007[14]	55/M		Kok et al. 1993[27]	13/F
	Tyvaert et al. 2004 (+SAH)[8]	47/F		Münch et al.1985[28]*	67/M
	Prekates et al. 2002[15]	53/F	Spinal cord	Ohno et al. 1990[29]	68/M
	Ojeda et al. 2001[16]	48/M		Na et al. 2010[30]	39/F
	Nishino et al. 1999[17]	59/M			
	Liou et al.1997[18]	27/M			

IVH, intraventricular hemorrhage, n.k., not known

* English full text is not available

The Five-Factors Score (FFS) [31] is one of the tools for considering the disease activity and prognosis, which includes cardiac involvement, gastrointestinal (GI) disease, renal insufficiency (creatinine > 1.6 mg/dl), proteinuria (>1 g/day) and CNS involvement. Guillevin et al. [31] stated increased FFS score indicates higher five-year mortality (FFS=0, mortality= 11.9%; FFS=1, mortality= 25.9%; FFS=2, mortality= 45.95%).

Corticosteroid is a considerablely effective therapy. In the report of Ribi et al., clinical remission could be induced by corticosteroid therapy alone in 93% of CSS patient with FFS=0 [32]. Cohen et al. reported that the patients with at least one poor-prognosis factor had lower rate of minor relapses in the group treated with corticosteroid plus 12-pulse cyclophosphamide than a 6-pulse regimen [33]. Complete remission rates and severe side effects of therapy were comparable for both groups [33]. Disease-free survival and event-free survival rate were higher in 12-pulse group[33].

In our patient, coronary vasculitis is not detected by angiography. Endomyocardial fibrosis is confirmed by cardiac echo. Biopsy of right ventricular endocardium showed eosinophilic and lymphocytic infiltration. We assumed that the elevation of cardiac enzymes is related to eosinophilic endomyocarditis or cardiac embolism. Possible explanation of ischemic stroke may be cardiac embolism, vasculitis or hypercoagulation. Because of higher FFS score (FFS>2) and suspected cardioembolism, we treated the patient with corticosteroid, cyclophosphamide and anticoagulant. There was a good response to these combined therapies. In conclusion, we found a tendency of middle-aged women predominance in CSS patient with subarachnoid hemorrhage and intracerebral hemorrhage is seen more in young and middle-aged male adults. Further investigation is needed. CSS can be an etiology of stroke, especially for patients with multiple cerebral infarcts and hypereosinophilia. Timely and effective treatment can prevent further complication.

Table 2. Infarct or gliosis of cerebral and/or cerebellar hemispheres in CSS patients

Reference	Age/Gender	manifestation	Eosinophil	ANCA	Neuroimaging	Exam findings	Treatment
Tanaka et al. 2011[35]	77/F	truncal ataxia	52.1%	p-ANCA(-)	MRI: infarct in the right cerebellum	MRA & carotid ultrasound:negative	corticosteroid
Sairanen et al. 2011[20]	49/M	left hemiplegia & hemihypoesthesia; dysarthria	42%	p-ANCA(+); c-ANCA(+)	MRI: infarct with hemorrhagic transformation in right basal ganglion and corona radiata	transcranial Doppler sonography: right-sided microemboli; TTE: minor ASD	corticosteroids; cyclophosphamide
Wolf et al. 2010[3]	61/M	n.k.	36%	c-ANCA(+)	n.k.	n.k.	n.k.
	67/M	n.k.	68%	p-ANCA(-); c-ANCA(-)	n.k.	n.k.	n.k.
	45/F	n.k.	21%	p-ANCA(-); c-ANCA(-)	n.k.	n.k.	n.k.
Twardowsky et al. 2010[22]	7/M	chorea	69%	p-ANCA(-); c-ANCA(-)	MRI: bilateral gliosis at the subcortical white matter and semioval center	EEG and cardiac echo: normal	IVIG; corticosteroid; cyclophosphamide
Ghaeni et al. 2010[34]	77/F	hypotonic tetraparesis; disoriented; aphasia	63.7%	p-ANCA(+)	MRI: multiple bilaterally cerebral and cerebellar infarctions	TEE & cervicocranial CTA: negative; Skin biopsy: positive	corticosteroid; cyclophosphamide
Bhagirath et al. 2008[23]	30/M	mental change, right hemiparesis, expressive aphasia	21%	p-ANCA(-); c-ANCA(-)	CTA: occlusion of the left middle cerebral artery bifurcation	TTE: no evidence of cardioembolism	corticosteroid; cyclophosphamide
Dinc et al. 2000[25]	46/F	cortical blindness	16%	p-ANCA(-); c-ANCA(-)	MRI: bilaterally occipital hemorrhagic infarctions	Doppler ultrasound & TEE & TTE: negative	prednisolone; cyclophosphamide; LMWH
Kok et al. 1993[27]	13/F of limbs	chorea; hypotonia	32.6%	n.k.	MRI: hyperintense images in both globus pallidus and in the subcortical white matter	TTE; negative; skin biopsy: positive	cyclophosphamide; corticosteroid

n.k.,not known; LMWH, low molecular weight heparin; MRA, magnetic resonance angiography; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; ASD, atrial septal defect; IVIG, intravenous immunoglobulin; CTA,computed tomographic angiography; EEG, electroencephalogram

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