



Multiple Cerebral Infarctions as an Initial Manifestation of Systemic Lupus Erythematosus with Concomitant Hypereosinophilic Syndrome

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Abstract

A 51-year old woman with drowsy consciousness and weakness in bilateral upper and lower extremities was admitted to our hospital. Laboratory test on admission showed eosinophilia, proteinuria, hypoalbuminemia, and elevated creatine kinase-MB. She also had positive antinuclear antibody, anti-ribonucleoprotein antibody and anti-Smith antibody as well as decreased levels of complements. Brain MRI showed multiple cerebral infarcts in both hemispheres. Renal biopsy determined class IV lupus nephritis. Vasculopathy and hypercoagulopathy induced by systemic lupus erythematosus rarely concomitant with hypereosinophilic syndrome were considered as main causes of multiple cerebral infarctions in this patient. The symptoms and laboratory data were gradually recovered with an intravenous methylprednisolone pulse therapy followed by oral prednisolone and monthly intravenous cyclophosphamide therapies.

Keywords: Hypereosinophilic syndrome; Systemic lupus erythematosus; Cerebral infarction; Lupus nephritis; Prednisolone; Cyclophosphamide

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder that commonly affects the nervous system. In 1999 the American College of Rheumatology (ACR) defined a standardized nomenclature system for 19 different neuropsychiatric syndromes associated with SLE [1]. The reported prevalence of cerebrovascular disease among SLE patients is close to 5% [2], and approximately 24% of patients with neuropsychiatric SLE (NPSLE) initially present with neurological signs [3].

However, on the whole, patients with SLE uncommonly have stroke as their initial manifestations. The pathogenesis of cerebral infarctions in patients with SLE is assumed to be vasculopathy caused by vasculitis, several autoantibodies, and secondary factors such as infections and side effects of immunosuppressants [4].

The traditional definition of hypereosinophilic syndrome (HES) was presented in 1975, which was consisted with three components; blood eosinophilia of $\geq 1500/\mu\text{l}$ persisting for more than six months, no other apparent etiologies for eosinophilia such as parasitic infections or allergic diseases, and signs and/or symptoms of eosinophil-mediated end-organ dysfunction. However, this definition has been considered to have several limitations, like that some HES patients require therapeutic interventions before six-month reassessment of eosinophilia to prevent life-threatening conditions.

To address these limitations, the evolving definition of HES integrates diseases in which eosinophils play a central role in pathogenesis, while taking pathogenic heterogeneity into consideration [5]. In 2012, experts reached consensus on terminology of hypereosinophilia (HE) [6]. HES is defined as blood eosinophils >1.5

$\times 10^9/\text{L}$ on two examinations separated in time by at least one month and/or tissue HE. HES are newly defined as HE (as defined above) with eosinophil-mediated organ damage and/or dysfunction, provided other potential causes have been excluded [6]. There are three subclassified groups according to pathogenic mechanism; primary HES, secondary HES, and idiopathic HES.

HES is well known for its hypercoagulable condition. Coagulation disorders are frequently observed in patients with HES. The association of SLE with HES has rarely been reported, furthermore there is only report describing a case of cerebral infarction possibly induced by HES in a patient with SLE to date. We describe an extremely rare case of SLE with HES, initially manifesting with multiple cerebral infarctions.

Case Report

A 51-year-old woman was transferred to our emergency department from her primary care physician because of suspected acute myocardial infarction, based on creatine kinase-MB (CK-MB) elevation without chest pain or dyspnea. The past medical history was only hypercholesterolemia well-controlled with atorvastatin for five years without any side effects. The patient never had any other abnormalities in a blood test and urinalysis checked every year. Furthermore, the patient had no history of asthma and allergy as well as no significant family history.

On arrival at our hospital, the patient was slightly drowsy [12 out of 15 points in Glasgow Coma Scale (E3V4M5)]. Physical examination determined that the patient had edema of the periorbital region and dorsal feet bilaterally, implying a possibility of hypoalbuminemia or congestive heart failure. No lung or heart abnormalities were found on the auscultation and the patient showed no signs of motor or sensory impairment. No skin abnormalities including palpable purpura were observed.

Laboratory tests in serum showed that white blood cell was 13,600 with eosinophilia of 3450/ μ l (25.4%), elevated CK-MB (18.8 U/L) (total CK was 218 U/L), hypoalbuminemia of 2.5 g/dl, and elevated C-reactive protein (CRP) at 6.3 mg/dl. Although electrocardiogram and transthoracic echocardiogram did not reveal any significant signs of acute myocardial infarction, mild thickness of left ventricular myocardium was observed. Abdominal computed tomography showed hepatosplenomegaly and swelling of bilateral renal parenchyma.

On the morning of her second hospital day, the patient could not fully move her bilateral upper or lower extremities, and her level of consciousness had deteriorated. Magnetic resonance imaging (MRI) showed multiple cerebral infarcts in both hemispheres (Figure 1A, 1B), and magnetic resonance angiography revealed no vascular stenosis (Figure 1C).

No thrombi were found in the heart or carotid arteries by ultrasonography. The patient's eosinophil count in serum had climbed to 4080/ μ l (29.7%). Hypereosinophilia-induced hypercoagulopathy was suspected after the exclusion of the possibility of infection, treatment was started immediately with intravenous methylprednisolone pulse therapy (1000 mg/day) for three days, followed by 50 mg of oral prednisolone (PSL) (1 mg/kg/day) and intravenous heparin administration. The two days after starting treatment the consciousness of the patient became clearer, and her bilateral paralysis, hepatosplenomegaly, renal swelling, and serum levels of eosinophil, albumin, CK-MB and CRP began to improve (Figure 2).

Laboratory tests submitted on admission revealed that positive results for anti-nuclear antibody (320-fold, homogenous pattern), anti-ribonucleoprotein antibody and anti-Smith antibody, in combination with elevated immune complex-C1q and decreased levels of complements (C3, C4 and CH50). The test results of myeloperoxidase and proteinase 3 anti-neutrophil cytoplasmic antibodies, cryoglobulin, lupus anticoagulant, anti-cardiolipin antibody, anti- β 2-glycoprotein I, antithrombin III, protein C, and protein S were all normal.

Since hypoalbuminemia and proteinuria were evident on admission (1.8 g/day), renal biopsy performed seven days later since initiation of prednisolone (PSL) therapy and the result showed class IV lupus nephritis (LN) with active lesions based on the classification system established by the International Society of Nephrology and Renal Pathology Society [7].

The interstitial nephritis was also observed, which implied the presence of eosinophil infiltration. The diagnosis was SLE with concomitant HES, and with multiple cerebral infarcts. Given that the patient had a prominent neurological symptom, the diagnosis of NPSLE was appropriate based on ACR classification [1].

In addition, eosinophilic infiltrations of the heart, liver, spleen, and kidneys might be present. We reassessed electrocardiogram and echocardiogram in two weeks and the results showed the diffuse inverse-T waves on V3-V4 and hypokinesis of left ventricular apex, respectively.

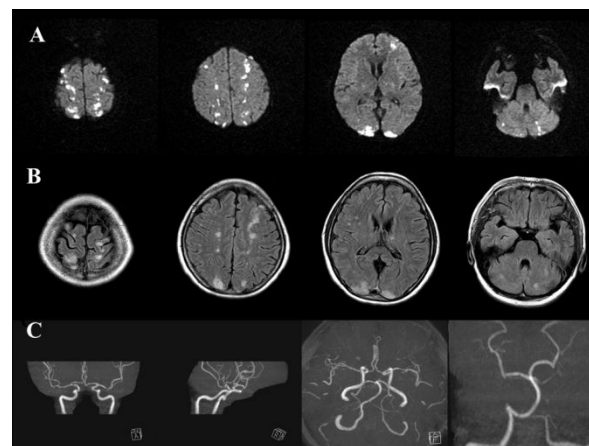


Figure 1: MRI of brain; (A) Diffusion-weighted image and (B) Fluid attenuated IR (FLAIR) image showing multiple bilateral cerebral infarcts in both hemispheres (C) Essentially normal MR angiography.

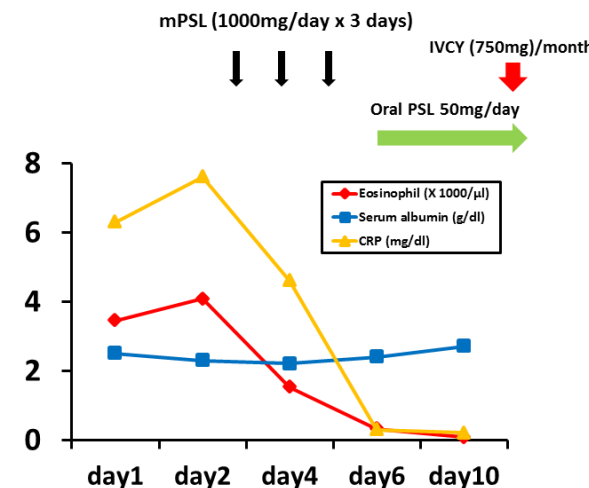


Figure 2: Transition of the laboratory data after the initiation of treatment. mPSL: methylprednisolone; IVCY: Intravenous Cyclophosphamide; PSL: Prednisolone; CRP: C-Reactive Protein.

These results also implied the presence of eosinophilic cardiomyositis. Treatment with monthly intravenous cyclophosphamide (IVCY) (750 mg/month) was added to oral PSL. Although mild nausea was observed during the IVCY treatment, no significant side effects were observed.

After total 6 months of the treatment, IVCY was switched to tacrolimus (1.5 mg/day) as a maintenance therapy and oral PSL has gradually been reducing to 8 mg/day. To date, no recurrence of SLE or HES was evident for 15 months.

Discussion

Although cerebral infarction is a representative neurological finding in NPSLE, it is relatively uncommon as an initial manifestation of SLE.

Antiphospholipid syndrome (APS) is the strongest preposition in the occurrence of cerebral infarction in patients with SLE, but in our case, the possibility of APS was excluded based on the normal results of lupus anticoagulant, anti-cardiolipin antibody and anti- β 2-glycoprotein I.

The pathogenesis of NPSLE is thought to be vasculopathy mainly caused by vasculitis and several autoantibodies such as anti-ribosomal P antibodies, anti-neuronal antibodies, and anti-phospholipid antibodies. Vasculitis was considered to be as a main cause of vasculopathy in patients with SLE, but previous reports suggested that true vasculitis contributed to neurological findings were rarely found in patients with NPSLE [8]. Basically, cerebral specimen obtained from brain biopsy is necessary to confirm a diagnosis of cerebral vasculitis. However, in this case the biopsy was not recommended because the symptoms rapidly deteriorated, which demonstrated that an early initiation of therapy was necessary. Another possibility which affects vasculopathy in this patient was accelerated atherosclerosis caused by inflammation as well as a long-history of hyperlipidemia. However, since the patient remarkably recovered after the induction of steroid and cyclophosphamide therapies, the contribution of atherosclerosis to the onset of multiple cerebral infarctions in this case seemed to be very small.

Arterial and venous thromboses are clinical entities in SLE with the prevalence over 10% and should be considered in this case. Reported causes of thrombosis in patients with SLE include high levels of circulating immune complexes, antiphospholipid antibodies, and hypercoagulation induced by hypoalbuminemia due to LN. Indeed, the patient in this case showed class IV LN with proteinuria (1.8 g/day), suggesting the possibility of which LN accelerates a formation of thrombosis even though no thrombosis were detected in the heart and cervical arteries.

Besides SLE, case reports of vasculopathy and hypercoagulation disorders associated with HES have increased in number in the past two decades [6]. Possible pathological mechanisms of eosinophil-induced hypercoagulability include endothelial damage caused by peroxidase release and the stimulation of platelet activation and aggregation by proteins contained in their granules, such as eosinophil cationic protein and major basic protein [9,10]. Furthermore, platelet-activating factor induces the activation of platelets, leukocytes, and endothelial cells [11].

To date, it has rarely been reported the cases of SLE concomitant with HES [12]. To our knowledge, there is only report published by Habibagahi et al. showing a cerebral infarction in a patient with SLE and HES [13]. The authors presented a case of 34 year-old female patient with lacunar infarction resulting from SLE concomitant with HES. Similar to our case, the patient had left and right ventricular obliteration with fibromatous biventricular endothelial thickening, possibly caused by HES. Although SLE sometimes causes eosinophilia, especially when the disease activity is very high, the level of eosinophilia is usually mild and rarely causes severe organ damages. In addition to a significant higher level of eosinophilia in this case, the eosinophil infiltration could occur in multiple organs such as heart, liver, spleen, and kidney in this case, strongly suggesting that this case was not simple SLE with eosinophilia. The biopsy specimen at least from one organ such as liver, heart or kidney should have been taken,

but the disease deterioration did not allow us to perform. The exact mechanisms of eosinophilia and HES in patients with SLE still remain unclear, but secondary factors such as certain infections may relate to the condition.

Conclusion

We concluded that the patient's multiple cerebral infarctions were the initial manifestation of both SLE and HES, both of which promote vasculopathy and hypercoagulopathy. Although we could not identify thrombi in the heart or cervical arteries, the combination of SLE-associated vasculopathy possibly induced by vasculitis and the presence of eosinophil proteins that are toxic to the endothelium, such as peroxidase, might have played a significant role in this case.

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