Mod Rheumatol (2001) 11:151–154

CASE REPORT

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Central retinal vein occlusion and cerebellar infarction complicating systemic lupus erythematosus: a case report

Received: May 15, 2000 / Accepted: January 15, 2001

Abstract We treated a 17-year-old woman who had systemic lupus erythematosus (SLE) complicated by central retinal vein occlusion (CRVO) and bilateral cerebellar infarction in the absence of demonstrable antiphospholipid antibodies. General fatigue, diffuse polyarthralgia, malar rash, and fever had developed during the 2 weeks preceding admission. The patient was diagnosed with SLE based on the presence of pleuritis, oral ulceration, pancytopenia, and antinuclear antibodies. Despite intravenous pulse therapy with methylprednisolone, blindness developed in the left eye and bilateral cerebellar infarcts were evident on magnetic resonance images. Fluorescein angiography revealed extensive retinal venous thrombosis leading to widespread retinal vein leakage, and a diagnosis of CRVO.

Key words Central retinal vein occlusion · Cerebellar infarction · Systemic lupus erythematosus

Introduction

Ocular manifestations of systemic lupus erythematosus (SLE) are not rare, and may include conjunctivitis, episcleritis, uvetitis, retinitis, central retinal artery occlusion, and central retinal vein occlusion (CRVO).[1,2] Although retinal vascular lesions are generally the most common ocular manifestation of SLE, CRVO with visual loss occurs occasionally. Severe retinal vasoocclusive events have been associated with active SLE, particularly SLE with central nervous system (CNS) involvement.[3–5] This association may reflect a pathogenetic mechanism similar to that involved in the microangiopathies which occur in patients with SLE.[3] A coagulation state involving antibodies against phospholipids such as cardiolipin and the lupus anticoagulant (LAC) has also been reported to lead to retinal vascular occlusion in SLE.[6] We report the case of a patient with SLE complicated by CRVO and cerebellar infarction in the absence of circulating antiphospholipid antibodies or LAC.

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Case report

A 17-year-old woman was admitted to our hospital with fever and malar rash on July 19, 1995. The patient had been well until 2 weeks earlier, when fever, oral ulceration, and polyarthralgia developed. On admission, the patient was somnolent. Marked erythema accompanied bilateral painful ulcers, 2 cm in diameter, of the buccal mucosa. The cranial nerves were intact. Tendon reflexes in the lower extremities were symmetrical, and no abnormal reflexes were elicited. Laboratory findings included normocytic anemia (hemoglobin (Hgb) 9.3 g/dl), leukocytopenia (white blood cell (WBC) count 2800/μl), thrombocytopenia (platelet count 9.7×10^4/μl), and an increased erythrocyte sedimentation rate (140 mm/h; the normal value is less than 10 mm/h, Westergreen). Other laboratory abnormalities included the elevation of serum aspartate aminotransferase (1226 U/l), alanine aminotransferase (419 U/l), lactate dehydrogenase (4186 U/l), and C-reactive protein (4.6 mg/dl). The serum concentration of total protein was low at 5.6 g/dl, while that of creatinine was high at 1.8 mg/dl. Serum complement components showed the C3 concentration to be slightly low at 24.6 mg/dl (normal range 79–135 mg/dl), while C4 was also low at 5.7 mg/dl (normal range 18–44 mg/dl). The plasma concentration of immunocomplex (C1q) was within the normal range. Urinalysis showed proteinuria semiquantitatively graded as 3+, while microscopic findings included 10–20 WBC, one to two hyaline casts, and one to two granular casts per high-power field. The serum concentration of IgA was high at 405 mg/dl (normal range 135–340 mg/dl), and that of IgG was high at 1568 mg/dl (normal

range 780–1480 mg/dl). The serum concentration of IgM was within the normal range. Urinary protein excretion was 0.5 g over 24 h. A test for antinuclear antibodies was positive at a titre of 1:5120, with a diffuse pattern. The value of double-stranded DNA antibodies was high at 53.7 IU/ml (the normal value is less than 7 IU/ml). Antibodies to Sm and ribonucleoprotein (RNP) antigens were absent, as were LAC, anticardiolipin (IgA, IgG, and IgM isotypes), and anti-β2-glycoprotein-I antibodies. The coagulation profile was normal, including an activated partial thromboplastin time (APTT) of 34 s (normal range 30–50 s). LAC were absent, and APTT and thromboplastin inhibition times were normal. The plasma concentrations of protein C, protein S, and antithrombin III were within the normal ranges. The concentration of D-dimer was high at 444 ng/ml (the normal value is less than 150 ng/ml), and that of thrombin–antithrombin (TAT) complex was high at 26 ng/ml (the normal value is less than 3 ng/ml).

The patient was diagnosed as having SLE because of the malar rash, oral ulcers, serotitis, neurological disorder, hematological disorder, immunological disorder, and antinuclear disorder. Because the systemic lupus erythematosus disease activity index (SLEDAI) of the patient was significantly high (41), aggressive immunosuppressive therapy was begun following admission. The patient was treated with oral prednisone (60 mg/day) and warfarin (2 mg/day), followed by intravenous pulse therapy with methylprednisolone at 1 g/day for 3 consecutive days with a considerable improvement in the disease activity. After plasma exchange was performed on the 4th hospital day, the patient became comatose and responded only slightly to painful stimuli. Tendon reflexes in the lower extremities were symmetric, and no abnormal reflexes were found. The left pupil was dilated and reacted to light consensually, but not directly. Although computed tomography (CT) of the brain showed no abnormalities, bilateral cerebellar infarcts were demonstrated by magnetic resonance imaging (MRI) (Fig. 1). MRI of the brain showed neither demyelination nor any other evidence of infarction. On the following day, MRI of the brain remained unchanged.

A lumber puncture performed on the 5th hospital day showed normal cerebrospinal fluid except for the IgG index (Table 1). Treatment with warfarin was discontinued because of cerebellar infarction. The level of consciousness had improved by the 6th hospital day. After the patient became alert and oriented, muscle strength and tone recovered. Visual acuity was assessed as 20/20 in the right eye, but only light perception could be demonstrated in the left eye. The right fundus was normal, but the left fundus showed large, diffuse hemorrhages involving the nasal half of the macula; the macular region was also edematous (Fig. 2). In the arteriovenous phase, fluorescein angiography of the left fundus showed extensive areas of retinal nonperfusion and obliteration of the inferiotemporal, superiotemporal, and inferionasal retinal arteries. In the venous phase, fluorescein angiography showed extensive venous involvement,

Table 1. Spinal fluid examination

Appearance of fluid	Clear
Initial pressure	100 mmH_2O
Xanthochromia	(−)
Glucose	41 mg/dl
Total protein	40 mg/dl
Red cell count	0
IgG index	0.44

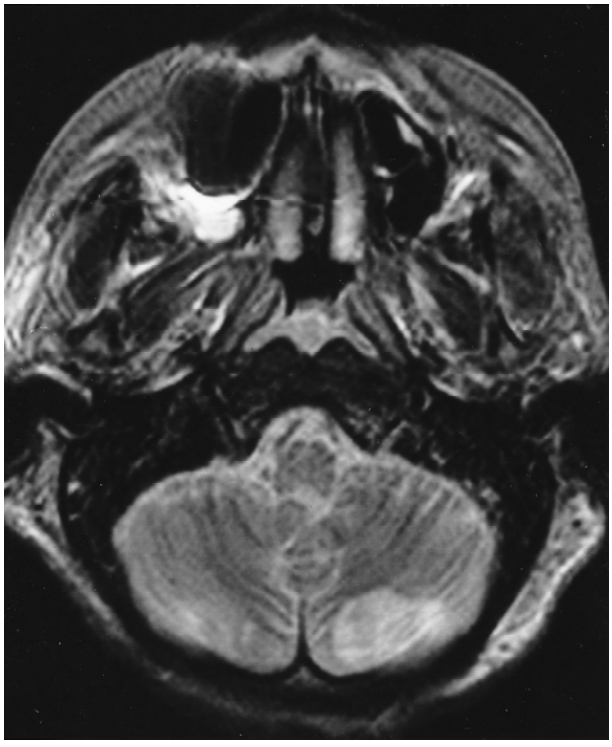

Fig. 1. T2-weighted magnetic resonance image of the brain showing areas of high signal intensity in both cerebellar hemispheres

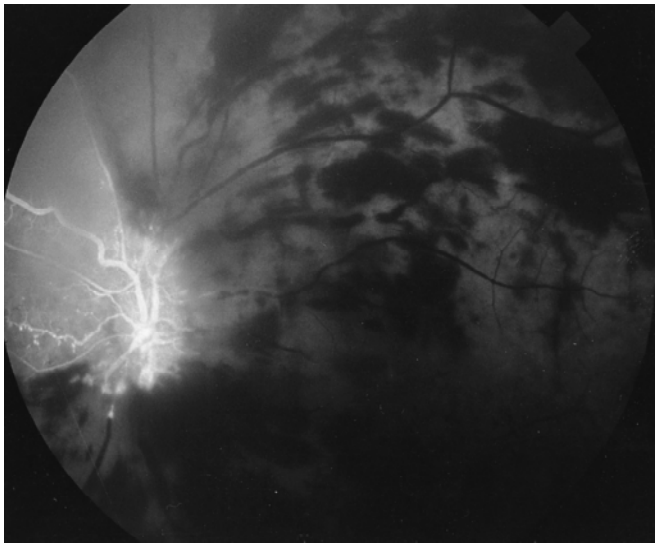

Fig. 2. The left fundus showed large diffuse hemorrhages in the nasal half of the macula as well as macular edema

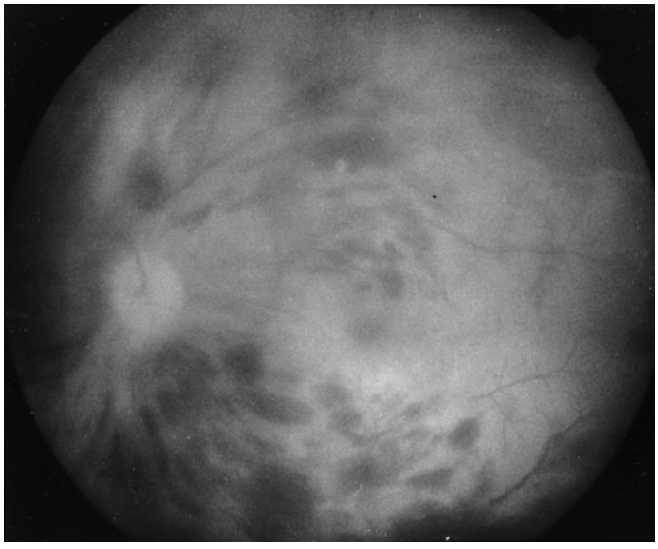

Fig. 3. Fluorescein angiography in the arteriovenous phase showed extensive nonperfusion of the retina and the obliteration of inferiotemporal, superiotemporal, and inferionasal retinal arteries

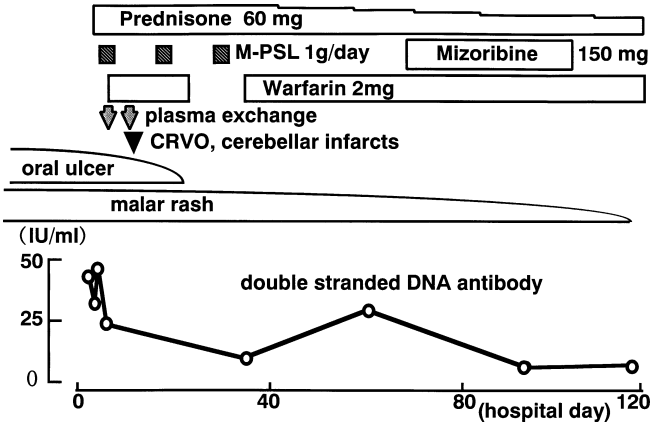

Fig. 4. Clinical course

with widespread leakage from the retinal veins (Fig. 3). These findings led to a diagnosis of CRVO. The patient was treated with panretinal photocoagulation to prevent further hemorrhage. Aggressive immunosuppressive therapy resulted in an improvement in the clinical symptoms and a decrease in serum double-stranded DNA antibodies (Fig. 4). The findings of a skin biopsy from cheek erythema showed severe vasculitis and a positive band test. A follow-up examination 100 days after the patient's initial presentation showed unchanged visual acuity and retinal findings consistent with central vein occlusion.

Discussion

SLE is an autoimmune disease involving multiple organs. As previously reported, ocular manifestations of SLE have been grouped into four main categories: cotton wool spots, retinal hemorrhages, minimal papilledema, and subretinal edema.[1] Given that this classification did not take account of pathogenesis, Vine and Barr[7] proposed another classification for retinopathy in SLE: focal retinal ischemia, severe retinal vascular occlusive disease, and proliferative lupus retinopathy. Proliferative lupus retinopathy, characterized by neovascularization, occurs in response to severe ischemia from the occlusion of major retinal vessels.

Retinal complications in SLE patients reportedly occur in 25%–30% of patients.[2,8] In a group of clinically stable SLE patients, fluorescein angiography showed that 26% had retinal abnormalities, including microaneurysms and fluorescein leakage.[9] Although retinal vascular lesions are the most common ophthalmic manifestations of SLE, severe retinal vasoocclusive disease is rare. Harvey et al.[2] reported that the prevalence of CRVO in SLE patients was 1.9%. The visual outcome of severe retinal vasoocclusive disease is often poor, and 55% of involved eyes have been reported to develop visual loss.[3] Although the frequency of CRVO in SLE patients is very low, SLE is relatively common among the systemic diseases inducing CRVO.[10,11]

The pathogenesis of retinal vasoocclusive disease complicating SLE remains obscure. In the present patient, CRVO probably occurred as a result of the vasculitis of SLE; three main reasons support this conclusion. First, the hallmark of SLE is vasculitis involving multiple organs, leading to many of the clinical manifestations of SLE. Bishko[12] has suggested that the infiltration of neutrophils and the proliferation of endothelial cells may cause obstructions in the retinal vessels in SLE. Moreover, Aronson et al.[13] have found depositions of immunoglobulins in the vascular layer of choroid capillaries, suggesting that ocular manifestations are associated with immune-complex vasculitis. In our case, the results of the skin biopsy from cheek erythema showed severe vasculitis with a positive band test. A second point suggesting vasculitis is that even though Derksen and Kater[14] reported that thrombosis occurs more frequently in patients with lupus anticoagulant than in those without, our patient lacked antiphospholipid antibodies. Coagulation parameters, including protein C, protein S, and AT III concentrations, were normal. The third point is that severe retinal vasoocclusive disease has been associated with increased SLE disease activity,[3,4] and CRVO occurred as part of a flare-up of SLE in our patient.

Importantly in our case, CRVO and the cerebellar infarctions developed at about the same time. Jabs et al.[3] reported that 73% of SLE patients with severe retinal vasoocclusive disease also had CNS lupus involvement. Johnson and Richardson[15] have suggested that the pathogenesis of CNS lupus involves the occlusion of small vessels, a pattern which is comparable to the small-vessel nature of retinal vasoocclusive disease. Therefore, the pathogenesis of CRVO and the cerebellar infarctions in our patient are likely to be similar.

A clouding of consciousness was a prominent feature in this case. This manifestation was not consistent with cerebellar infarctions and the finding of the spinal fluid test. Because immunosuppressive therapy resulted in an

improvement in the level of consciousness, we speculate that the somnolence in this case may have resulted from central nervous system lupus.

In our patient, treatment with prednisone was effective in controlling the activity of SLE. Pulido et al.[16] and Levine et al.[17] have reported that both corticosteroid and antithrombotic therapy reduce the recurrence of thrombosis such as retinal vasoocclusive disease in antiphospholipid syndromes. We suggest that prednisone might also prevent the recurrence of retinal vasoocclusive disease by ameliorating vasculitis in small vessels such as retinal veins. A combination therapy of prednisone with cyclophosphamid may be alternative way of preventing the occurrence of thrombosis such as CRVO in patients with severe SLE.

We have presented the case of a patient with SLE who simultaneously developed CRVO and bilateral cerebellar infarctions in the absence of coagulation abnormalities, including the antiphospholipid syndrome. A diagnosis of CRVO should be considered in a patient with active SLE, who presents with rapidly progressive visual loss accompanying CNS complications, even if antiphospholipids antibodies are absent.

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