Lupus Retinopathy Associated with a High IFN-α Level in the Cerebrospinal Fluid

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Abstract

An 18-year-old woman who presented with photosensitivity, butterfly rash and acute visual disturbance was diagnosed as SLE with retinopathy. The level of IFN-α in the cerebrospinal fluid (CSF) was markedly elevated. Her visual acuity recovered with high-dose prednisolone therapy. IFN-α in the CSF also reduced to within the normal range. The mechanism causing lupus retinopathy is not clearly understood. Although the association between lupus retinopathy and a high level of IFN-α has not been reported, the injection of IFN-α is known to frequently cause retinopathy in hepatitis patients. We discuss the possibility of IFN-α causing retinopathy in SLE patients. (Internal Medicine 41: 754-756, 2002)

Key words: SLE, cotton-wool spot, cytokine

Introduction

Retinopathy is a well-known complication of systemic lupus erythematosus (SLE), with an incidence of 7-26% (1). The precise mechanism for the development of lupus retinopathy is not clearly understood. However, most patients with SLE who present with acute visual loss have retinal or choriocapillary ischemia from vasculitis or occlusion. There are two possible mechanisms for the development of lupus retinopathy. In some patients, the manifestations are associated with complement-dependent vasculitis, while in others, they are associated with anti-phospholipid antibodies (1-4).

Abnormal serum levels of several cytokines in SLE have been reported in addition to abnormalities of spontaneous or stimulated cytokine production by peripheral blood mononuclear cells in vitro. These cytokines are profoundly involved in disease activity, and modulate the manifestations of SLE. Recently, Shiozawa et al reported that a high concentration of IFN-α in the cerebrospinal fluid (CSF) is associated with lupus psychosis (5). This cytokine may be produced in the brain, because it was detected in neurons and microglia by immunohistochemistry (5).

We treated a case of lupus retinopathy with a high level of IFN-α in the CSF. In this report, we discuss the possibility that IFN-α may also be involved in the development of lupus retinopathy.

Case Report

An 18-year-old girl, who had a low-grade fever, butterfly rash, and photosensitivity, had been treated with a non-steroidal Chinese herbal drug (saira-to) and steroid ointment at another clinic since 1998. She noticed a visual disturbance, and was admitted to our hospital in November 2000. On admission, a butterfly rash was observed on her cheeks. However, hair loss, oral aphtha, and ringed erythema were absent. She had no history of headache, nausea, consciousness disturbance or any symptoms suggesting thrombosis. Laboratory investigations yielded the following results: WBC 5.21×10^9/l, Hb 10.6 g/dl, and platelets 289×10^9/l. The erythrocyte sedimentation ratio was remarkably elevated at 129 mm/h. Anti-nuclear and anti-dsDNA antibodies were elevated (×640; speckled and 32.9 IU/ml, respectively). Hypocomplementemia was not found (CH50, 35.8 U/ml). However, the level of circulating immune complex was elevated (5.0 IU/ml; normal<2.9). Serum IgG was also elevated (3,302 mg/dl). A remarkable prolongation of the APTT (91.1 seconds) and a biological false-positive syphilis test were present. IgG type of anti-cardiolipin antibody was elevated (1.7; normal<1.0), but the IgM type was not elevated (1.0; normal<1.0). Both anti-cardiolipin-GPI antibody and lupus anticoagulant were negative (2.2 U/ml and 1.28, respectively). Proteinuria was not found, and urinary sedimentation was normal. Her corrected visual acuity in the left eye worsened to 6/20. Funduscopy revealed cotton-wool spots, microhemorrhages, and retinal avascular areas in both eyes, especially in the left eye (Fig. 1). She had no history of diabetes mellitus or hypertension. We diagnosed her as having SLE with retinopathy. She met four of the American College of Rheumatology criteria for SLE. She did not have any symptoms that suggested CNS lupus. There were no findings sug-
gestive of CNS lupus in MRI, 99mTc-HMPAO single-photon emission computed tomography or electroencephalogram. A lumbar puncture revealed a mild elevation of lymphocytes (13/3 μl) and IgG (7.9 mg/dl) in the CSF. Though the intrathecal IL-6 level was within normal range (3.690 pg/ml; normal range 0.221-4.62), the IFN-α level in the CSF was remarkably elevated (194 IU/ml; normal range<6.0 IU/ml). Her serum IFN-α was within the normal range. We treated her with methylprednisolone pulse therapy (1,000 mg×3 days). Thereafter, she was treated with high-dose prednisolone (60 mg/day) accompanied by warfarin. Her symptoms and laboratory data improved gradually with therapy. The IFN-α level in the CSF declined and eventually became undetectable. Her corrected visual acuity in the left eye improved to 20/20. She was discharged in March 2001.

Discussion

Retinopathy, including cotton-wool spots, hemorrhages, retinal detachment, and vasculitis, is a well-known complication of SLE. In these cases, visual ability is reported to have an excellent prognosis, while blindness has been reported in some cases (6, 7). However, retinopathy in SLE is a marker of a poor survival prognosis (3). Complement-dependent vasculitis is believed to be the most important process in the pathogenesis of lupus retinopathy. However histological evidence of immune complex-mediated vasculitis has been reported in a few cases (2). Anti-phospholipid antibody is thought to be another candidate, because SLE patients with retinopathy have antiphospholipin antibody more frequently than those without retinopathy (1, 3). Asherson et al observed 7 cases of occlusive vascular disease affecting retinal and choroidal vessels among 84 patients with SLE and anti-cardiolipin antibody (8). Giorgi et al classified lupus retinopathy into two categories: Hughes’ retinopathy, which is caused by antiphospholipid-induced retinal vascular thrombosis, and “classic” retinopathy, which involves vasculitis or atherosclerosis (4). The former may accompany central retinal artery occlusion, retinal artery or vein occlusion frequently, while the latter shows cotton-wool spots with or without retinal hemorrhage, neovascularization or microaneurysm. The present case showed cotton-wool spots but not retinal vessel occlusion. Therefore, our case may be classified as “classic” retinopathy rather than the anti-phospholipid antibody-induced retinopathy.

Inflammatory cytokines including IL-6, IL-8 and IFN-α have been shown to be elevated in CNS lupus. Increased levels of IL-6 (88% of the CNS lupus patients) (9), IFN-α (29%) (5) and IL-8 (100%) (9) were detected in the CSF. These data suggest the crucial role of these cytokines in pathogenesis of CNS lupus. The present case had markedly elevated intrathecal IFN-α but not IL-6. It has been reported that IFN-α is increased in the CSF of lupus patients with psychosis (83.3%) in comparison to CNS lupus without psychosis (0%), and it is thought that IFN-α synthesized in the brain may cause psychosis (5). However our case did not show psychosis. A variety of clinical autoimmune-like diseases have been reported in patients receiving exogenous IFN-α. In hepatitis C patients, IFN-α therapy not only induces psychosis, but also causes retinal lesions frequently (57.1%) (10). Most of the retinal lesions are tiny and heal spontaneously without subjective symptoms despite continuous administration of IFN-α. It is thought that IFN-α induces retinopathy by means of vasospasm, thrombosis, or deposition of immune complexes in the retinal vasculature (11, 12). Funduscopic findings of IFN-α associated retinopathy differ from those of Hughes’ retinopathy, however, they closely resemble the findings of “classic” retinopathy. Therefore it is difficult to distinguish “classic” retinopathy from IFN-α associated retinopathy with funduscopy. These findings suggest that a high level of endogenous IFN-α may play some role in inducing retinopathy in the present case, like exogenous IFN-α.
in hepatitis C patients. Our case indicates that IFN-α may cause lupus retinopathy. Although most IFN-α associated retinopathy heals spontaneously despite continuous administration of IFN-α, the retinal lesion in our case did not. This difference may come from the fact that subcutaneously administered IFN-α quickly disappeared from blood ($T_{1/2}$: 3.4 hour; when $50 \times 10^6$ U of IFN-α was administered) and most part did not migrate into CSF (IFN-α concentration in serum/CSF ratio ranged from 550:1 to 1,100:1) (13). The intrathecal production of IFN-α could be the result of an inflammatory process primary or secondary to brain tissue damage. The cellular origin of IFN-α production in the brain remains unknown, but both neurons and microglial cells have the capacity to produce this cytokine.

It has been reported that 73% of cases with lupus retinopathy accompany CNS lupus (3). Structural similarities between the retinal and cerebral vessels have been discussed as a reason why lupus retinopathy frequently complicates CNS lupus (14). However, the high level of IFN-α in the CSF of lupus patients with psychosis and in the present case suggest a new reason for the high frequency of these complications. IFN-α synthesized in the brain may have the potential to cause both psychosis and retinopathy.

An extensive search of the literature revealed that this is the first report to evaluate the IFN-α level in lupus retinopathy. Further measurements of IFN-α in lupus retinopathy may confirm this relationship.

References