Systemic Lupus Erythematosus

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Case report

A 54-year old Caucasian woman was admitted to the Massachusetts General Hospital for renal failure and changes in mental status. Her previous medical history was significant for hypertension. She was diagnosed by non-caseating granuloma on lung biopsy and treated with PO steroids for presumed sarcoidosis eight months prior to the admission. She also was hospitalized twice for sepsis and once for renal failure in a local hospital. Her ocular symptoms started 2 months after the lung biopsy had been done. At that time she complained of blurry vision in both eyes and was told by a local ophthalmologist that she had retinal lesions caused by sarcoidosis and steroid induced diabetes. In addition to the mental status changes and renal failure she also presented with pericardial effusion, rash, arthritis, and pancytopenia.

On the initial eye exam she was confused and yelled words at random. Her husband stated that her major complains included joint pain, rash, hair loss, and blurry vision OU. The visual acuity was 20/50 and 20/70 right and left eye, respectively. Intraocular pressure was normal OU. External eye exam and anterior segment with portable slit lamp did not show any pathology. Indirect ophthalmoscopy revealed cotton wool spots in the posterior pole and multiple dot/blot hemorrhages OU (**Figure 1**), consistent with retinal findings in patients with systemic lupus erythematosus (SLE), polyarteritis nodosa or Wegener's granulomatosis. An extensive serologic work-up was requested by us.

After ruling out sepsis, treatment with IV Solumedrol pulse 1000 mg/day for three consecutive days was administered by the rheumatologist. The patient responded with slight overall improvement. However, after discontinuation of IV Solumedrol, her medical status deteriorated again. It became clear that the disease was steroid responsive, but more aggressive immunosuppressive treatment was contraindicated because of pancytopenia with agranulocytosis on bone marrow biopsy. Therefore, the patient continued IV Solumedrol 80 mg/day and Immunology and Uveitis Service suggested treatment with plasmapheresis or intravenous immunoglobulin (IVIg). Plasmapheresis was declined by other specialists because of a lack of indication and low amount of immune complexes on kidney biopsy. Therefore, treatment with IVIg 200 mg/kg/day for five consecutive days was initiated as the patient's medical status deteriorated further.

However, continual deterioration of symptoms was observed after five days of treatment with IVIg as well. The MRI of the brain revealed lacunar infarcts and T2 densities consistent with vasculitis. The visual acuity dropped to 20/65 OD and 20/100 OS. In addition to previous symptoms the patient developed dyspnea and pulmonary hemorrhage was diagnosed. The pancytopenia had improved, which allowed administration of cyclophosphamide IV pulse 750 mg. No improvement was noticed after the pulse. The results of blood tests revealed elevated levels of antinuclear antibodies (ANA), surface interleuikin-2 receptor, circulating immune complexes assay, alpha-1-acid glycoprotein, and decreased C3 complement levels, confirming a severe autoimmune disease. Diagnosis of SLE was proposed based on the clinical symptoms and laboratory findings. The Immunology and Uveitis Service recommended again staged sequential plasmapheresis followed by Cyclophosphamide IV pulse. After several days of discussion plasmapheresis for 5

consecutive days followed by cyclophosphamide IV pulse 750 mg has been administered. The patient's overall medical status improved dramatically. She became capable of fluent communication, the levels of creatinine decreased, and her visual acuity improved to 20/30 OD and 20/40 OS. The patient was discharged to a rehabilitation center and planned for cyclophosphamide IV pulse every month. She died of cardiac tamponade in a local hospital three months later.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is defined as a chronic, systemic, immunologically mediated disease. This definition would fit with several other autoimmune diseases, e.g. rheumatoid arthritis, Wegener's granulomatosis, mixed connective tissue disease, etc. Nevertheless, the diagnostic criteria for SLE are more specific. The diagnosis is made by the presence of four or more of

1. malar rash
2. discoid rash
3. photosenzitivity
4. oral or nasopharyngeal ulcers
5. nonerosive arthritis
6. serositis
7. renal disorder
8. neurological disorder
9. hematological disorder
10. immunological disorder
11. presence of antinuclear antibodies

Regrettably, ocular involvement is neglected in the criteria. Therefore a patient with arthritis, leukopenia, renal failure, and ocular involvement, as in the above reported patient, is not diagnosed with SLE. Consequently, appropriate treatment and monitoring is delayed and the generally poor prognosis of SLE becomes even worse in such cases.

Epidemiology

The incidence of SLE has been estimated between 1.8 and 20 cases per 100.000 per year. Approximately 90% of patients are women. In fact, one out of 1000 women suffers from SLE. The incidence of SLE in black women is approximately four times higher than in white. Systemic lupus erythematosus is more frequent in Asian women as well. The usual onset of SLE is between 15 and 45 years of age.

Individuals with HLA-DR2 and HLA-DR3 genes are more susceptible to the disease. More than 50% of patients present with complement gene deficiencies. Several trigger factors for SLE has been detected. These include: microbes, drugs, chemicals, and sunlight.

Pathogenesis

Dysfunction in immune regulation plays the principal role in the pathogenesis of SLE. Hyperreactivity of B-cells, producing a spectrum of autoantibodies, is primarily responsive for the immune dysregulation, although T-cells are involved in the pathogenesis as well. The tissue injury is caused by immune complexes, deposition of which induces cell infiltration and damage to the tissue by proteolytic and collagenolytic enzymes.

Histopathology of affected tissue reveals vasculitis with fibrinoid necrosis and deposition of immunoglobulin and complement in small vessels and capillaries. Renal involvement begins with

deposition of immune complexes in the glomeruli. Mesangial proliferation, glomerular necrosis, hyaline thrombus formation, and interstitial damage determine the severity of kidney disease.

Laboratory manifestation

Patients with SLE produce wide spectrum of autoantibodies. Approximately 95% of them produce ANA. ANA as well as other antibodies produced in patients with SLE can be seen in other systemic diseases, but antibodies to double-stranded DNA (anti-ds DNA) and anti-Sm antibodies to polypeptides that complex with certain species of nuclear RNA are quite specific for SLE. The activity of the disease can be monitored by the levels of ANA, complement, cryoglobulins, and circulating immune complexes measured by the Raji cells assay. The serum levels of soluble interleukin-2 receptor (CD25), CD27, and CD30 molecules have been shown to be elevated prior to the exacerbation of clinical symptoms.

Systemic manifestation

The patients with SLE may present with various systemic manifestations. The general symptoms include: fever, malaise, arthralgias, myalgias, headache, and loss of appetite and weight.

Although almost in all cases deposits of immunoglobulin are found in the glomeruli, only one half has clinical nephritis. Urine analysis of asymptomatic patients often shows hematuria and proteinuria. Renal failure and sepsis are two main causes of death in patients with SLE.

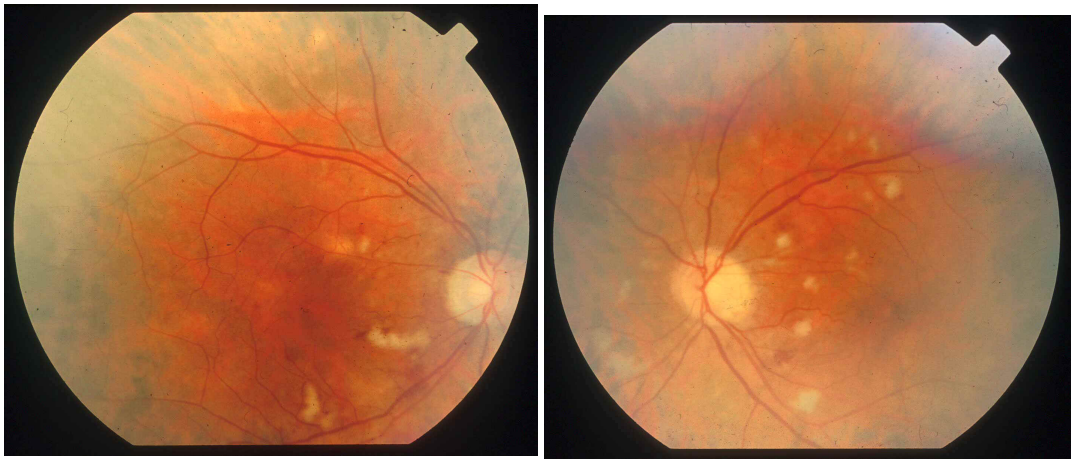
Between 70 and 80% of patients develop skin lesions during the course of disease. Approximately 20% of them have skin lesions as an initial presentation. The pathognomonic lupus or butterfly rash across the nose occurs in only 30% of patients with SLE. The acute lupus rash may be present elsewhere. Discoid or disc-shaped skin lesions, pathognomonic for discoid lupus, can manifest also in SLE. Photosensitivity rash can appear even after mild sun exposure. Livedo reticularis, a reddish purple rash, is usually present in patients with severe vasculitis or in individuals with elevated antiphospholipid antibodies. Alopecia with patchy or diffuse loss of hair with scalp scarring is another skin manifestation. Raynaud's phenomenon can cause bluish discoloration of digits and blanching of the skin.

Neurological manifestations of lupus are reported in 25 to 75% of patients and can involve all parts of the nervous system. One study showed that the incidence of elevated antiphospholipid (APL) antibodies in patients with neurological symptoms is approximately two times higher than in those without neurological symptoms. Moreover, APL antibodies antedated neurological symptoms in 81% of patients.

Pregnant women with SLE are at higher risk of spontaneous abortions, stillbirths or fetal retardation. Congenital lupus, caused by maternal antibodies crossing the placenta, may be another consequence of SLE during pregnancy.

Ocular manifestation

The most common ocular manifestation of SLE is keratoconjunctivitis sicca (KCS), occurring in approximately of 25% of patients. Conjunctivitis, interstitial keratitis, episcleritis, and diffuse or nodular scleritis are less common. The severity of episcleritis and scleritis may closely mirror the activity of systemic disease. Necrotizing scleritis is rare in patients with SLE.



Retinal involvement in SLE is the second most common ocular manifestation after KCS. The classic finding in lupus retinopathy is the cotton-wool spot, which has been correlated with avascular zones on fluorescein angiography. The histopathological findings include infiltration of vessel walls with fibrillar material causing vascular constrictions and widespread hyaline thrombus formation. Typically, the vessel walls are free of inflammatory cells. Therefore, it is not considered as a true vasculitis. Immunofluorescence staining reveals deposition of IgG with C1q and C3. It was shown that 88% of patients with lupus retinopathy have active systemic disease and a significantly decreased survival rate. Therefore, close monitoring and aggressive treatment of these patients is critical. Uveitis, though rare, may occur also in the absence of retinal involvement.

Choroidopathy is much less common in SLE than is retinopathy. Transudation of fluid through Bruch's membrane may result in multifocal RPE and serous retinal detachments. Although more extensive pathological findings are seen in the choroid as compared to retina, they appear to be subclinical.

The neuroophthalmological manifestations of SLE are associated with damage to the optic nerve and brain, most likely as a result of the ischemic process. However, a clinical picture similar to optic neuritis are reported as well.

Treatment

Between 20 and 30% of patients with SLE have only mild disease. Thus, nonsteroidal antiinflammatory drugs are sufficient in controlling the activity of disease in this group of patients. Dermatological changes usually well respond to hydrochloroquine (Plaquenil). Patients on chronic Plaquenil must be monitored semiannually for ocular toxicity.

Acute exacerbation of SLE is usually treated with a combination of high-dose intravenous therapy, high dose oral steroids and an immunosuppressant. Cyclophosphamide seems to be the most effective immunosuppressive drug in treatment of SLE. Staged sequential plasmapheresis followed by cyclophosphamide IV pulse as well as intravenous immunoglobulin showed some promising results in controlling the exacerbation of the disease. In a recent study, two patients with SLE refractory to conventional treatment have been successfully treated with immunoablative high-dose cyclophosphamide.

Prognosis

The ten-year mortality in SLE is 71%. Renal failure and septicemia are the main causes of death. One study showed that long term treatment with cytotoxic agents such as cyclophosphamide can preserve visual acuity better than 20/30. Since ocular symptoms are not included in the diagnostic criteria and the mortality rate is extremely high, it is critical that ophthalmologists recognize patients with a suspicion of SLE and make an appropriate arrangement for the treatment and monitoring. It is also critical that rheumatologists and other specialists do not neglect ocular manifestations, thus providing an earlier diagnosis in some patients and better monitoring of activity of the disease.

Reading list:

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