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Effects of IV cyclophosphamide on HIV viral replication in a patient with systemic lupus erythematosus

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ABSTRACT

Several cases of patients with concomitant SLE and HIV infection have been reported in the literature; however, the effect of immunosuppressive therapy on HIV replication has not been described. We present the case of a 46 y/o woman with a ten-year history of HIV infection who was treated with IV cyclophosphamide for SLE nephritis. She had a positive HIV Western Blot just a few months before the diagnosis of SLE. Serum levels of HIV RNA had been persistently non-detectable since the assay became available. The patient was not receiving any antiretroviral therapy, raising doubts about the diagnosis of HIV infection. After 3 pulses of IV cyclophosphamide, HIV RNA levels went up to 135,720 copies/ml. Shortly after discontinuation of therapy viral levels were again undetectable. This case shows one of the possible clinical scenarios in patients with coexistent HIV infection and SLE. In our patient SLE appears to provide some immunologic defense against viral replication. Cross-reactivity of autoantibodies with HIV proteins may play a role in this mechanism. Effective immunosuppressive therapy suppresses this protection and leaves the immune system vulnerable to HIV reproduction. Treatment in these cases can be difficult and should be individualized in an attempt to achieve a balance between control of viral infection and SLE activity.

Introduction

The coexistence of systemic lupus erythematosus (SLE) and HIV is an unusual but clinically interesting situation. There have been 26 reports of the co-occurrence of these conditions in the medical literature. Possible reasons for this low incidence have been discussed elsewhere (1). In the majority of these cases there is clinical and serologic improvement in SLE after infection with HIV, probably related to qualitative and quantitative effects on Th cells. The following case was previously reported on in 1996 as part of a report on the co-occurrence of SLE and HIV (2); further developments during the management of the patient's SLE over the past 3 years have made this subsequent report necessary.

Case presentation

A 46-year-old Hispanic female, HIV positive for several months, presented to our institution in August 1989 with a 3-month history of generalized malaise, low-grade fever, arthralgias, malar rash, photosensitivity, alopecia, and weight loss. Her risk factor for HIV was her husband's intravenous drug abuse. Physical examination revealed a temperature of 102.4°F, malar rash, painless oral ulcers, and generalized lymphadenopathy. The initial laboratory workup was significant for a creatinine of 0.8 mg/dL; hematocrit 25%; and a sedimentation rate of 120 mm/hr. ANA titer was 1/2560; anti-dsDNA titer, 1/640; the C3 level was 39 mg/dL (normal range 83 - 177 mg/dL); and the C4 level 8 mg/dL (normal range 15 - 45 mg/dL). Urinalysis showed no protein with normal sediment. Western blot done for confirmation of HIV status was positive and the CD4 count was 561/mm^3.

A diagnosis of SLE was made based on the available clinical and laboratory evidence. Prednisone was started with clinical remission of SLE. At the end of the first year of follow-up, she developed a creatinine of 1.4 mg/dL with a proteinuria of 2,200 mg/day. Renal biopsy revealed diffuse proliferative lupus nephritis (WHO class IV). AZT was started and prednisone was increased to 40 mg/day. Creatinine serum levels normalized to 0.8 mg/dL. Prednisone was slowly tapered over the next 4 1/2 years to 4 mg/day. The patient did well clinically, albeit with persistent proteinuria of 1 - 1.5 g/day, but no elevation in serum creatinine.

By March 1995, the complement levels had normalized. Anti-cardiolipin antibodies and lupus anticoagulant were not detected. An ANA panel showed the presence of anti-Scl 70 and anti-RNP antibodies, although there was no clinical evidence for either systemic sclerosis or mixed connective tissue disease. The patient was kept on AZT, Epivir, and low dose prednisone. Over the next 3 years she suffered two lupus "flares" manifested as fever, malar rash, and joint pains; both episodes were associated with the abrupt withdrawal of steroids.

On September 1996 the first HIV RNA assay of the patient's blood revealed an

HIV viral load below detectable levels. Similar results were confirmed on 7/97 and 10/97. Her CD4 cell count at this time was 1404/mm^3. Due to the above mentioned findings, the possibility of a false positive test for HIV associated with the presence of SLE was considered, and anti-retroviral therapy was discontinued.

On December 1997, she was admitted to the hospital with a bacterial pneumonia. Appropriate antibiotics were started and her prednisone dose was increased to 20 mg/day. The pneumonia was successfully treated but a deterioration in renal function was noted (creatinine 1.5 mg/dL) and was associated with cellular and granular casts in the urine, 5324 mg/day of urine protein, and decreased complement levels.

A second renal biopsy was done that was consistent with a diffuse proliferative glomerulonephritis (WHO class IV). Activity and chronicity scores were moderate. There was no evidence of HIV associated nephropathy. Creatinine increased to 2.4 mg/dL despite prednisone 60 mg/day. A repeat HIV RNA assay was again non-detectable, and it was decided to treat the patient with IV cyclophosphamide. Pulses were given monthly starting on March 1998. Three days after the third pulse, an HIV RNA assay revealed 135,720 copies/dL. Cyclophosphamide was discontinued and the patient was kept on prednisone 20 mg/day. There was an initial improvement in serum creatinine (1.4 mg/dL), but after treatment was withheld it increased to 2.3 mg/dL and remained at this level. The amount of proteinuria improved to 2340 mg/24 hr. and serum complement levels normalized. A second RNA assay post-cyclophosphamide was done in late June 1998 showing 540 copies/dL.

Since then 4 other tests have been carried out, all of them showing non-detectable HIV RNA levels. Several CD4 counts have been performed with results ranging from 141 to 762/mm^3. A repeat ANA panel showed anti-RNP antibodies. Anti scl-70 has been consistently negative on repeat testing.

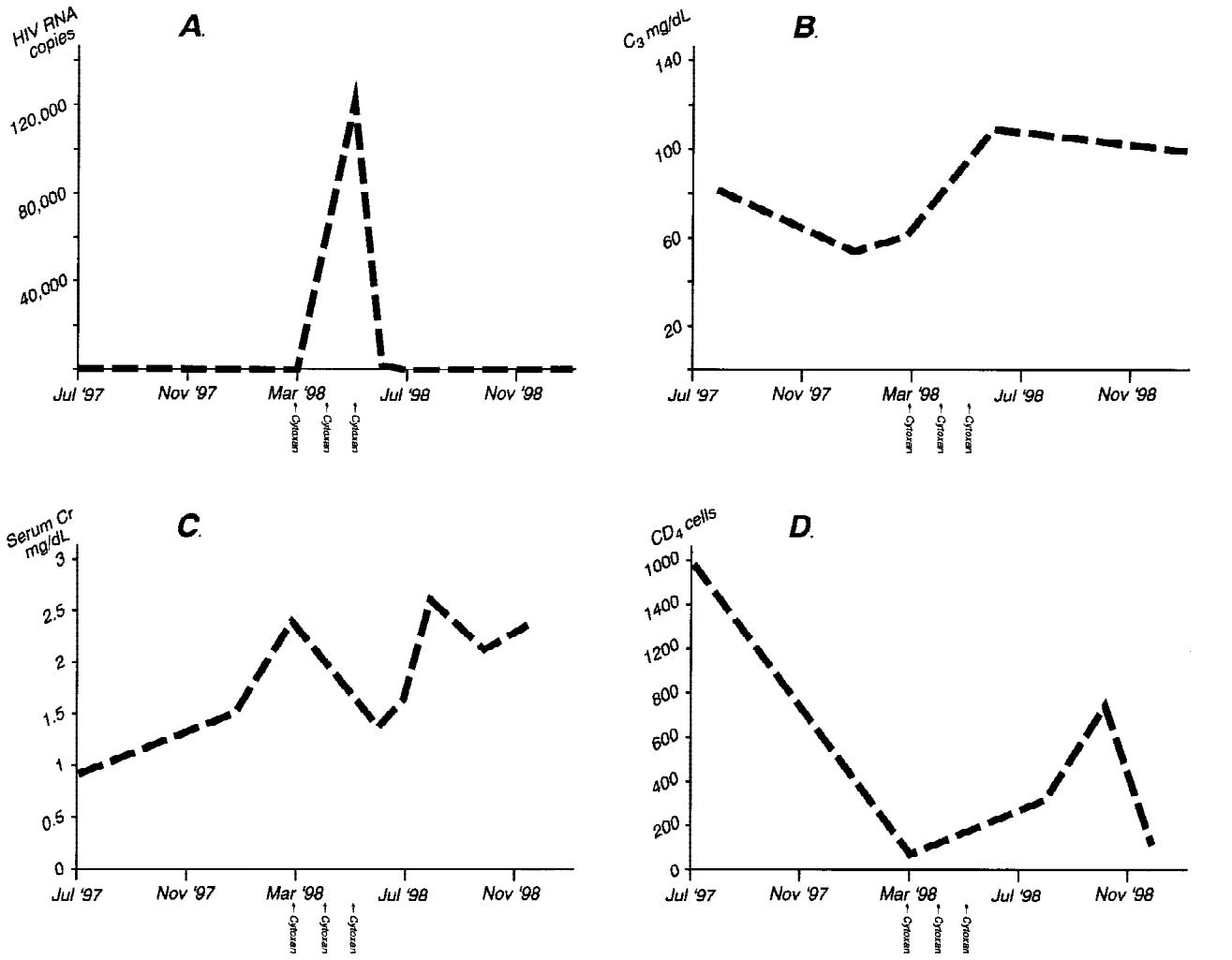

Fig. 1. The levels of HIV RNA, CD4, C3, and serum creatinine are compared over time and in relation to cyclophosphamide administration. We can see the increase in complement level, decrease in serum creatinine, and detection of HIV RNA after cyclophosphamide administration. The serum creatinine started to increase soon after discontinuation of cyclophosphamide. The dose of prednisone was increased from 20 mg/day to 60 mg/day on February 1998, and then decreased to 40 mg/day on March 1998 due to the occurrence of psychosis. It was kept at this level throughout the remainder of treatment. The reasons for the observed drop of CD4 cells by March 1998 could be related to the increased activity of SLE and/or to the presence of a bacterial pueumonia between 12/97 and 1/98.

Discussion

The clinical overlap between HIV and SLE rarely occurs. The effects of one disease on the manifestations of the other is a potentially fascinating area of inquiry. There is marked overlap in the characteristics of the immune response in both conditions including polyclonal B cell activation, T cell activation and T cell anergy. There is also increased production of Th2 and decreased production of Th1 cytokines with progression of the disease (3). Clinically, the manifestations of the diseases can at times be indistinguishable. Nevertheless, the ability to differentiate between the clinical activity of the two diseases is critical as treatment options vary considerably and treatment for one condition may worsen the other.

The use of laboratory tests or pathologic specimens may be helpful in this situation although uncertainties abound. A patient with SLE can have a false positive ELISA and indeterminate Western Blot (4), while HIV infection can be associated with antinuclear antibodies and anticardiolipin antibodies. The ANA titers in these cases are usually less than 1:160 and no anti-double stranded-DNA antibodies are observed (5). The antiphospholipid antibodies are not associated with any of the established clinical manifestations of the antiphospholipid syndrome (6). As mentioned in the introduction, several authors have reported the suppression of SLE by HIV. In one case by Furie (7), there was reappearance of lupus clinical activity following initiation of AZT therapy.

After at least 10 years of infection with the virus, our patient had non-detectable levels of viral RNA in her blood. In addition, she had not developed any opportunistic infections associated with HIV. Contrary to the previous observations, in our patient the SLE showed significant activity while there was non-progression of HIV infection. Two important considerations come to mind. First, did the presence of HIV have a role in the development of SLE ? The role of retroviruses as possible triggers of SLE has been supported by several lines of evidence, including the importance of endogenous retroviruses in the mouse model of SLE, the detection of retroviral antibodies, antigens, and virus sequences in the organs and sera of SLE patients, and the electron microscopic detection of unknown retrovirus particles in the organs of SLE patients (3). Ranki (8) studied the presence of antibodies to HTLV-1 and HIV-1 in patients with connective tissue disease. Forty-six percent of the patients showed antibodies to one or more proteins, while only 2.7% of control serum showed antibodies. None of the sera showed immunoblot reactivity diagnostic of HTLV-1 or HIV infection. Thirty percent of the sera reacting with retroviral proteins did not react with any of the ribonucleoproteins (RNP, Sm, SS-B, Scl-70). However, a role of the retrovirus in SLE and other connective tissue diseases remains to be proven. Secondly, is the immune dysregulation associated with SLE responsible for the suppression of HIV infection in our patient ? Substantial antibody cross-reactivity has been found between the autoimmune antigen 70 K (one of the dominant epitopes of the RNP antigen) and neutralizing epitopes of gp 120/41 (HIV envelope glycoprotein complex) (9).

Douvas *et al.* studied the sera of 9 mixed connective tissue disease patients with anti-RNP antibodies (10). Five of the sera were 70-99% effective in neutralizing the infectivity of one or more HIV-1 strains. Our patient had anti-RNP antibodies in her serum. This evidence raises the possibility of a protective role of some autoantibodies against HIV infection through a mechanism of molecular mimicry.

Another interesting observation in our case was the rapid return of HIV RNA to undetectable levels after termination of cyclophosphamide pulses even on 40 mg of prednisone daily. This is indirect evidence of a very effective immune response against viral replication.

The physician needs to consider the diagnosis of HIV in a patient presenting with an SLE-like clinical syndrome. When the diseases co-occur, treatment needs to be individualized in an attempt to achieve a balance between control of the viral infection and SLE activity.

This case demonstrates one of the possible interactions between these two diseases in which the autoimmune process predominates and may be suppressing the viral infection.

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