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Human immunodeficiency virus in a cohort of systemic lupus erythematosus patients

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Abstract

Background: Systemic lupus erythematosus (SLE) and acquired immunodeficiency syndrome (AIDS) share many clinical manifestations and laboratory findings, therefore, concomitant diagnosis of SLE and human immunodeficiency virus (HIV) can be challenging.

Methods: Prospective cohort with 602 patients with SLE who attended the Rheumatology Clinic of the Hospital de Clínicas de Porto Alegre since 2000. All patients were followed until 01 May 2015 or until death, if earlier. Demographic, clinical and laboratory data were prospectively collected.

Results: Out of the 602 patients, 11 presented with the diagnosis of AIDS (1.59%). The following variables were significantly more prevalent in patients with concomitant HIV and SLE: neuropsychiatric lupus (10.9% vs. 36.4%; $p = 0.028$) and smoking (37.6% vs. 80%; $p = 0.0009$) while malar rash was significantly less prevalent in this population (56% vs. 18.2%; $p = 0.015$). Nephritis (40.5% vs. 63.6%; $p = 0.134$) and hemolytic anemia (28.6% vs. 54.5%; $p = 0.089$) were more prevalent in SLE patients with HIV, but with no statistical significance compared with SLE patients without HIV. The SLICC damage index median in the last medical consultation was significantly higher in SLE patients with HIV (1 vs. 2; $p = 0.047$).

Conclusions: Our patients with concomitant HIV and SLE have clinically more neuropsychiatric manifestations. For the first time, according to our knowledge, higher cumulative damage was described in lupus patients with concomitant HIV infection. Further studies are needed to elucidate this complex association, its outcomes, prognosis and which therapeutic approach it's best for each case.

Keywords: Systemic lupus erythematosus, Human immunodeficiency virus, Acquired immunodeficiency syndrome, Neuropsychiatric lupus, Opportunistic infections

Background

Concomitant diagnosis of systemic lupus erythematosus (SLE) and acquired immunodeficiency syndrome (AIDS) can be intriguing and challenging. SLE and human immunodeficiency virus (HIV) infection share many clinical manifestations, including musculoskeletal symptoms such as myalgia, arthralgia/arthritis, skin rashes, lymphadenopathy and organ involvement, such as kidneys, heart, lungs and central nervous system [1]. They also have several common laboratory findings such as anemia, leukopenia, lymphopenia, thrombocytopenia and hypergammaglobulinemia [1].

There are few studies assessing the clinical and laboratory manifestations in SLE patients with HIV infection, as well as patient's profile and their evolution. Furthermore, there are no studies assessing the prognosis of this association until now. Therefore, the present study aimed to demonstrate the profile of these patients in our center, appointing their clinical and laboratory features, the significant differences between the patients with or without HIV, the treatment offered and their evolution considering infections, other diseases and mortality.

Methods

Study population

This prospective cohort consisted of 602 SLE patients who attended the Rheumatology Clinic of the Hospital de Clínicas de Porto Alegre since 2000. All patients

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fulfilled the American College of Rheumatology (ACR) revised criteria for the classification of SLE [2] and an informed consent form was obtained from all participants. The patients were followed until 01 May 2015 or until death, if earlier. The demographic, clinical and laboratory data were prospectively collected.

Clinical and laboratory variables

The following variables were recorded: age, gender, age at diagnosis of SLE and HIV (when the last was positive), smoking status (current or previous), cardiovascular diseases, dyslipidemia, other autoimmune diseases and treatment performed. Clinical manifestations of SLE included the presence of photosensitivity, malar rash, discoid rash, oral or nasal ulcers, arthritis, serositis (pleuritis or pericarditis), nephritis and neurological disease, defined as seizures or psychosis. The assessment of the group of patients with concomitant HIV included infections, as well as CD4 and viral load at the diagnosis and the last count available. The laboratory evaluation included the presence of hematological disorders (hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia), positive antinuclear antibody (ANA) (titer > 1:80) or other autoantibodies such as anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, anticardiolipin (aCL), lupus anticoagulant and false positive VDRL. The patients were also evaluated in regard to secondary antiphospholipid syndrome and secondary Sjogren's syndrome, according to the classification criteria for both diseases [3, 4]. The SLEDAI and the SLICC damage index of the last medical consultation were recorded too, as a measurement of disease activity and cumulative damage, respectively [5].

Statistical analyses

A descriptive analysis of data through calculation of mean and standard deviation (SD) for quantitative variables was performed while the frequency and percentage were calculated for categorical variables. The median and interquartile range were calculated to quantitative variables with asymmetrical distribution. We used the chi square test or Fisher's exact test to compare categorical variables, and continuous variable were analyzed with Mann-Whitney test. All statistical analyses were performed using SPSS 20.0. All tests were performed at the 0.05 level of significance and were two-sided.

Results

Our study consisted of 602 SLE patients, 75.2% European derived, 92% female and 11 (1.59%) of these patients presented with HIV. The patients mean age was 42.8 ± 12.7 years and the mean SLE diagnostic age was 29.9 ± 13.9 years. Demographic, clinical and laboratory profile were showed in Table 1. The following variables were significantly more

prevalent in patients with concomitant HIV and SLE: neuropsychiatric lupus (10.9% vs. 36.4%; $p = 0.028$) and smoking (37.6% vs. 80%; $p = 0.0009$) while malar rash was significantly less prevalent in this population (56% vs. 18.2%; $p = 0.015$). The following features were more prevalent in SLE patients with HIV, but without to reach statistical significance compared with SLE patients without HIV: nephritis (40.5% vs. 63.6%; $p = 0.134$), hemolytic anemia (28.6% vs. 54.5%; $p = 0.089$), presence of anti-Ro (39.4% vs. 63.6%; $p = 0.125$) and anti-La (13.1% vs. 27.3%; $p = 0.172$), cardiovascular disease (18.1% vs. 36.4%; $p = 0.126$) and diabetes mellitus (7.7% vs. 18.2%; $p = 0.212$). Regarding the autoantibodies, in our cohort, amongst SLE patients with HIV, 72.7% had positive Coomb's test, 45.5% anti-dsDNA, 9.1% anti-Sm, 63.6% anti-Ro, 27.3% anti-La, 27.3% anti-RNP and 9.1% antiphospholipid antibodies. Hypergammaglobulinemia and hypocomplementenemia were observed in 81.8% of SLE patients with HIV.

The survival rate was 96.6% and 93.5% in 5 and 10 years, respectively, in SLE patients without HIV. Meanwhile, the survival rate was 90% in 5 and 10 years in SLE patients with HIV. There was no significant difference between the two groups. The SLICC damage index median in the last medical consultation was significantly higher in SLE patients with HIV (1 vs. 2; $p = 0.047$). The median of the last SLEDAI did not reach significant difference between groups (0 vs. 1; $p = 0.55$). In the HIV group, infections occurred in 54.5%, predominantly human papillomavirus infection, followed by tuberculosis and herpes zoster infection. Coinfection with C hepatitis virus occurred in two patients (18%).

Simultaneous diagnosis of SLE and HIV infection was done in one patient, while HIV following SLE was diagnosed in eight patients and HIV infection preceded SLE in two patients. All the patients were female and at diagnosis of HIV the mean CD4 count was 296 cells/ μ L and HIV-RNA 60.000 copies/ml. Antiretroviral therapy (ART) was taken by all the patients and, considering SLE, seven were treated with hydroxychloroquine (HCQ), two with azathioprine (AZA), two with cyclophosphamide (CYC), one with methotrexate (MTX) and one with mycophenolate mofetil (MMF), according to the severity of each case (Table 2).

Discussion

The coexistent infection of HIV and SLE is unusual and intriguing, because both diseases are characterized by multisystem involvement and immune dysfunction related to T lymphocytes, cytokine production alterations and polyclonal activation of B lymphocytes [6]. Despite these similarities, several theories have been formulated to explain the reason of the unexpectedly lower prevalence of concomitant diagnosis of HIV and SLE. SLE may prevent HIV infection as a result of polyclonal

Table 1 Demographic, clinical, and laboratory features of SLE patients with and without HIV infection

Patients features	All patients (n = 602)	SLE patients without HIV (n = 591)	SLE patients with HIV (n = 11)	P value ^a
Females	92% (602)	91.9% (591)	100% (11)	1.000
European derived	75.2% (584)	75.4% (573)	63.6% (11)	0.479
Smoking ^b	38.3% (582)	37.6% (215)	80% (11)	0.009
Obesity	25.3% (502)	25.9% (127)	0% (11)	0.074
Age (years)	48.2±14.9(597)	48.3±14.9 (586)	43.1±12.7 (11)	0.245
SLE age at diagnosis (years)	33.5±14.2 (591)	33.6±14.2 (580)	29.9±13.9 (11)	0.390
Malar rash	55.3% (597)	56% (586)	18.2% (11)	0.015
Photosensitivity	72.1% (598)	72.4% (587)	54.5% (11)	0.191
Oral ulcers	35.6% (598)	35.6% (587)	36.4% (11)	1.000
Arthritis	72.4% (597)	74.4% (586)	63.6% (11)	0.486
Serositis	25.2% (595)	25% (585)	36.4% (11)	0.482
Nephritis	40.9% (596)	40.5% (585)	63.6% (11)	0.134
Neurologic disorders	11.4% (596)	10.9% (585)	36.4% (11)	0.028
Psychosis	6.5% (597)	6.3% (586)	18.2% (11)	0.158
Seizures	6% (597)	6% (586)	9.1% (11)	0.498
Hematologic disorders	75.8% (598)	75.8% (587)	72.7% (11)	0.773
Hemolytic anemia	29.1% (598)	28.6% (587)	54.5% (11)	0.089
Leukopenia/Lymphopenia	55.9% (598)	56% (587)	45.5% (11)	0.549
Thrombocytopenia	21.4% (598)	21.5% (587)	18.2% (11)	1.000
Anti-dsDNA	46% (567)	46% (556)	45.5% (11)	1.000
Anti-Sm	20.8% (549)	21% (538)	9.1% (11)	0.474
Anticardiolipin	27.3% (550)	27.6% (539)	9.1% (11)	0.304
Lupus Anticoagulant	10% (548)	10.1% (537)	9.1% (11)	1.000
Anti-Ro	39.9% (516)	39.4% (505)	63.6% (11)	0.125
Anti-La	13.4% (515)	13.1% (504)	27.3% (11)	0.172
Anti-RNP	31.1% (515)	31.2% (504)	27.3% (11)	1.000
SLEDAI (median) ^c	1 (415)	1 (407)	0 (11)	0.550
SLICC damage index (median) ^c	1 (559)	1 (551)	2 (11)	0.047

Abbreviations: SLE systemic lupus erythematosus, SLEDAI systemic lupus erythematosus disease activity index, SLICC systemic lupus international collaborating clinics, HIV human immunodeficiency virus

^aChi square test for qualitative variables and Mann-Whitney test for quantitative variables

^bCurrent or past smoker

^cMedian (interquartile interval)

antibody stimulation [7] and treatment with antimalarials [8]. Patients with SLE have higher levels of interleukin (IL)-16 and IL-16 inhibits HIV infection in vitro, representing a possible protective role against HIV in SLE patients [9]. Likewise, SLE cannot develop in the setting of CD4 cell depletion seen in HIV [10]. Zandman-Goddard and Shoenfeld proposed that autoimmune manifestations in patients with HIV occur after the restoration of immunological competence (CD4 count > 500 cells/ μ L and low viral load) using ART or during the first stage of HIV (the acute HIV infection), when the immune system is intact and, hence, autoimmune diseases may present [11].

Kopelman and Zolla-Pazner published in 1988 the first report of a patient with HIV infection and SLE [12].

Since then, there have been several case reports or small case series of patients with concomitant SLE and HIV. Literature review has identified a total of 58 patients reported until 2014, some of which did not fulfill the criteria for SLE [1]. Then, in 2014, Mody et al. published a relatively large case series of 13 patients with coexistent HIV infection and SLE evaluated in a hospital of Durban, South Africa [1].

Kopelman and Zolla-Pazner have tested 151 consecutive patients with HIV and found that 19 had positive ANA, most of it in low titers, which usually is not associated with clinical manifestations of SLE [12]. Medina-Rodriguez et al. also found a significant number of HIV-positive patients with positivity for aCL IgG (94%), and aCL IgM (44%) [13].

Table 2 Demographic, clinical and laboratory features, treatment and outcome of SLE patients with HIV

Case	Gender	First DX	Clinical features	Autoantibodies	SLE treatment	ART	CD4 at DX ^a	Last CD4	Outcome
1	F	SLE	Discoid lupus, photosensitivity, oral ulcers and arthritis	ANA and anti-Ro	CS	Yes	434	337	Good health condition, but loss of follow-up in the Rheumatology Clinic
2	F	SLE	Raynaud, arthritis and vasculitis	ANA, anti-dsDNA, anti-Ro and anti-La	CS	Yes	572	205	Disseminated TB at 2015, follow-up in the Infectious Diseases Clinic
3	F	SLE	Arthritis, leucopenia, lymphopenia, alopecia, Raynaud and photosensitivity	ANA	HCQ	Yes	424	1056	SLE in remission, HIV controlled
4	F	SLE	Discoid lupus, photosensitivity, nephritis, leucopenia and lymphopenia	ANA	HCQ	Yes	149	524	HCV coinfection SLE in remission and HIV controlled
5	F	SLE	Photosensitivity, oral ulcers, arthritis and nephritis	ANA, anti-Ro and anti-La	CS, AZA → MMF and tacrolimus	Yes	273	991	Pulmonary TB in 2008, kidney transplantation in 2011
6	F	SLE	Photosensitivity, serositis and arthritis	ANA	None	Yes	172	391	HCV coinfection, SLE in remission and HIV controlled
7	F	SLE	Alopecia, arthritis, nephritis, hemolytic anemia and hypergammaglobulinemia	ANA, anti-dsDNA and anti-Ro	HCQ, CYC → AZA	Yes	321	165	Good initial response, poor adherence to treatment with posterior reactivation of nephritis and CD4 count drop
8	F	HIV	Hemolytic anemia, serositis, oral ulcers and arthritis	ANA, anti-Sm and anti-RNP	HCQ, MTX	Yes	NA	477	CMV Retinitis in 2006, SLE in remission and HIV controlled
9	F	HIV	Hemolytic anemia and nephritis	ANA and anti-dsDNA	CS, HCQ CYC → AZA	Yes	235	252	Complete response to CYC, posterior poor adherence and loss of follow-up due to drug addiction
10	F	SLE	Hemolytic anemia, serositis, leucopenia, lymphopenia, oral ulcers, arthritis and nephritis	ANA and anti-dsDNA	HCQ	Yes	203	323	SLE in remission and HIV controlled
11	F	Both	Alopecia, hemolytic anemia, nephritis, thrombocytopenia, leucopenia and lymphopenia	ANA	CS, HCQ →AZA	Yes	111	NA	Both diagnosed in hospital stay, progressing to death from sepsis

Abbreviations: *ACL IgG* anti-cardiolipin IgG, *ACL IgM* anti-cardiolipin IgM, *ANA* anti-nuclear antibody, *ART* active antiretroviral therapy, *AZA* azathioprine, *CMV* cytomegalovirus, *CS* corticosteroids, *CYC* cyclophosphamide, *dsDNA* anti-double-stranded DNA, *DX* diagnosis, *F* female, *HCQ* hydroxychloroquine, *HIV* human immunodeficiency virus, *M* male, *MMF* mycophenolate mofetil, *MTX* methotrexate, *NA* not available, *SLE* systemic lupus erythematosus, *TB* tuberculosis

^aCD4 cell count at diagnosis of HIV-infection: cells/mm³

However, Petrovas et al. in a case-control study that compared the prevalence of antiphospholipid antibodies in patients with HIV infection, SLE with or without antiphospholipid syndrome (APS) and in primary antiphospholipid syndrome (PAPS), also evaluating the reactivity of these antibodies with β 2-glycoprotein (GPI). It was demonstrated that the prevalence of aCL antibodies in HIV-infection was 36%. However, anti- β 2-GPI occurred in only 5% of HIV, which seems to reduce its thrombogenic potential [14]. Therefore, antiphospholipid antibodies occur in HIV-1 infection, but are not associated with thrombosis [14]. In our cohort, prevalence of

antiphospholipid antibodies did not differ between patients with and without infection by HIV.

Additional studies evaluated the presence of other autoantibodies in HIV-positive patients and found multiple autoimmune phenomena HIV-associated, many of those seen in SLE, including besides the presence of ANAs, antiplatelet antibodies, antilymphocyte antibodies and antineutrophil cytoplasmic antibodies (ANCA), as well as Coomb's positivity, circulating immune complexes, rheumatoid factor and cryoglobulins [7, 13, 15, 16]. Furthermore, the presence of antibodies to extractable nuclear antigens (ENA) has also been described, although with controversial findings. Muller et al. have tested the

presence of ENA by enzyme-linked immunosorbent assay (ELISA) in 100 HIV-positive patients, detecting anti-dsDNA, anti-histone, anti-Sm, anti-RNP and anti-Ro in 45% to 90% of these patients [17]. In its turn, Lafeuillade et al. in a study including 119 HIV-positive patients, found a lower frequency of those autoantibodies (4% had ANAs, 1% anti-dsDNA, 4% anti-Sm and 6% anti-histone) [18]. Thus, the presence of these autoantibodies in HIV patients is still controversial. Variations in the studied populations and in the analysis techniques employed explain, in part, these discrepancies [19]. In one study, the positivity for autoantibodies was significantly associated with lower CD4 lymphocyte counts and with increased mortality, which can indicate a prognostic implication of the autoimmunity in the context of HIV infection [15].

In patients with coexistence of HIV infection and diagnosis of SLE, three patterns of disease occurrence have been described: HIV following SLE diagnosis, SLE following the diagnosis of HIV infection and simultaneous diagnosis of HIV and SLE [20]. In our cohort, the most prevalent pattern was the one in which patients with established SLE were subsequently diagnosed with infection by HIV. Some studies suggest that HIV infection can attenuate the natural history of SLE [10, 21–23]. On the other hand, the impact of SLE in patients with pre-existing HIV infection is not well known. Some authors propose that SLE may contribute to a worst outcome of the HIV infection, keeping in mind that there are some reports describing a shorter time span until the development of AIDS in patients with concomitant SLE [23]. Nonetheless, this data is unavailable in many cases and there are some reports in which patients with coexistence of HIV infection and SLE did not developed AIDS even after long periods of observation [19]. Furthermore, some authors believe the immunologic effects of SLE and HIV may antagonize each other, contributing to the uncertainty regarding the clinical impact of this association [23].

Many of the clinical features of SLE overlap with either the primary features or secondary complications of HIV infection [24]: dermatologic findings such as alopecia, oral ulcers and facial rash; constitutional symptoms, including fever and malaise; musculoskeletal involvement such as arthralgias, arthritis and myalgias; renal abnormalities, including hematuria and proteinuria; central nervous system disorders, such as seizures and psychosis; hematologic alterations, including anemia, leucopenia, lymphopenia and thrombocytopenia; and immunologic features such as hypergammaglobulinemia and positive ANA [21, 25]. The term *pseudolupus* has been used to describe patients with HIV infection that present with rheumatic manifestations similar to SLE. In our cohort, nephritis, neuropsychiatric lupus, hemolytic anemia, hypergammaglobulinemia, presence of anti-Ro and anti-

La were the most prevalent features amongst the SLE patients infected by HIV.

Besides, false positive HIV on ELISA tests have also been described in SLE patients, making the diagnosis even more difficult, and making it necessary to perform other confirmatory tests for HIV [26]. In these cases, viral RNA PCR assays were superior than the p24 antigen assay (less sensitive) to exclude the possibility of a false positive HIV on ELISA test [27]. Low complement due to HIV infection has not been reported. Therefore, hypocomplementenemia may be a helpful test to differentiate lupus activity from HIV-related manifestations [24]. In our cohort the majority of patients with AIDS presented with hypocomplementenemia and this finding contributed not only to assess the disease activity, but also to establish the diagnosis of SLE.

The treatment of patients with coexistent SLE and HIV infection is challenging and there aren't well established therapeutic guidelines thus far. Immunosuppressive medications may have a negative impact in patients with preexistent impaired immunity [25]. However, with the adequate suppression of the HIV viral load, it is postulated that the treatment of SLE would not anticipate the development of AIDS [19]. Associated to ART, HCQ seems to be a reasonable and safe approach, considering it also has antiviral properties in HIV patients [28] and that its anti-inflammatory effect doesn't appear to be associated with an increased risk of opportunistic infections [29]. Low-dose corticosteroids may be considered with caution for those with severe immunosuppression by AIDS [25]. Relative safety of using MMF in HIV-positive patients has been confirmed by its successful use in the solid organ transplantation in HIV patients on ART [30]. Therefore, the risks and benefits have to be considered carefully when deciding the therapeutic approach that is more adequate to each patient with concomitant HIV infection and SLE [20]. Patients of our cohort that used CYC for the induction treatment of nephritis, followed by maintenance with AZA, developed a complete response with no major infectious complications.

It is well known that there is an increased risk of opportunistic infection in SLE patients, as well as in patients infected by HIV and this is the leading cause of morbidity and mortality in both diseases [6]. In our cohort, survival in 5 and 10 years was similar in SLE patients with or without AIDS. Even though we emphasized a statistically significant difference in the SLICC, indicating a greater cumulative damage in patients with concomitant AIDS, the clinical and prognostic relevance of this finding is uncertain thus far, once there was no significant difference in the survival rate between the groups in our study population.

Special attention must also be paid to infections caused by *Mycobacterium tuberculosis*, due to its high prevalence in HIV patients [31] as well as SLE, especially

in developing countries [32]. Patients with lupus and HIV seems to have a higher risk of developing tuberculosis as shown by the largest case series available on the subject, in which 7 out of 13 patients were diagnosed with tuberculosis [1]. In our cohort, only 2 patients infected by HIV developed tuberculosis, probably reflecting the demographic differences and the regional prevalences of this disease.

Conclusion

Patients with concomitant HIV and SLE presented with neuropsychiatric manifestations more often. Therefore, it is essential to pay attention to the early diagnosis of HIV, especially in the scenario of this severe manifestation and in light of the need to intensify the immunosuppression. Moreover, there was a higher prevalence of hypergammaglobulinemia and hypocomplementenemia, which in turn, can be an useful tool to identify disease activity. For the first time, higher cumulative damage was described in lupus patients with concomitant HIV infection, which can contribute to a worst life quality and reduction of the survival rates, although further studies are needed to elucidate this complex association, its outcomes and prognosis.

Abbreviations

aCL: Anticardiolipin; ACR: AMERICAN College of Rheumatology; AIDS: Acquired immunodeficiency syndrome; ANA: Antinuclear antibody; ANCA: Antineutrophil cytoplasmic antibodies; APS: Antiphospholipid syndrome; ART: Antiretroviral therapy; AZA: Azathioprine; CYC: Cyclophosphamide; ds-DNA: Anti-double-stranded DNA; ELISA: Enzyme-linked immunosorbent assay; ENA: Extractable nuclear antigens; GPI: Glicoprotein; HCQ: Hydroxychloroquine; IL: Interleukin; MMF: Mycophenolate mofetil; MTX: Methotrexate; PAPS: Primary antiphospholipid syndrome; SD: Standard deviation; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC: Systemic Lupus International Collaborating Clinics

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All the authors collaborated in the analysis and in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre, and an informed consent form was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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