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CASE BASED REVIEW

Systemic lupus erythematosus and HIV infection: a whimsical relationship. Reports of two cases and review of the literature

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Abstract Systemic lupus erythematosus (SLE) is rarely reported in association with HIV infection. We describe two unpredictable cases and provide a review of the literature. Retrospective analysis of the medical records of two HIV-infected patients diagnosed with SLE and admitted at Luigi Sacco Hospital (Milano, Italy). Search of the literature from 1981 to 2012 and review of the cases reported. Case 1: a 32-year-old HIV-infected African woman who developed a SLE flare after re-introduction of antiretroviral therapy (ART). The flare was characterized by bullous skin eruption and membranous glomerulonephritis. Case 2: a 44-year-old Caucasian woman, admitted to our hospital because of lacunar stroke: HIV infection and SLE were simultaneously diagnosed. Literature: 55 cases of SLE in the setting of HIV infection were reported. Forty-five patients met the requirements of the American College of Rheumatology for the diagnosis of SLE. The diagnosis of SLE preceded HIV infection in six patients. On the contrary, in 29 patients, HIV infection was reported before SLE. Median CD4+ count at SLE diagnosis was 361 cells/μl. A SLE manifestation following ART immune recovery was documented in 18.2% of the cases. On the contrary, the progression of HIV infection paralleled with SLE remission in 22.5% of the patients. The study shows that an autoimmune disease such as SLE can occur despite the loss of immunocompetence caused by HIV infection. Moreover, SLE and HIV infection influence each other possibly through immunologic mechanisms determining awkward manifestations.

Keywords Combined antiretroviral therapy · HIV infection · Immune reconstitution inflammatory syndrome · Systemic lupus erythematosus

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Introduction

The coexistence of HIV infection and systemic lupus erythematosus (SLE) is a rare but noteworthy event, because it provides an interesting glimpse into the pathogenesis of these two conditions. Moreover, it represents a diagnostic and therapeutic challenge: the overlapping manifestations and the immunosuppressive treatment of immunodeficient patients call for a deeper understanding of this biological paradox. We will describe two cases and provide a review of the literature.

Methods

We retrospectively reviewed the clinical records of two HIV-infected patients, admitted at Luigi Sacco Hospital (Milano, Italy), who received a diagnosis of SLE.

In order to identify previously published cases of patients with a diagnosis of HIV and SLE, we searched the English medical literature from 1981 to 2012 using the following

PubMed and Medline keywords: "systemic lupus erythematosus," "HIV," and "AIDS". Continuous variables are presented as medians with interquartile ranges. Categorical variables are presented as frequencies and percentages of the specified group. Comparisons between groups were made with the Fisher exact test or Kruskal–Wallis test as appropriate. A two-sided p value of <0.05 was considered statistically significant.

Results

Case 1

A 32-year-old African woman with known seropositivity for HIV since 2003 (CDC stage B2) was admitted in 2012 at Luigi Sacco Hospital because of fever, weight loss, and chest pain. Antiretroviral therapy (ART) had been introduced in 2003. In 2007, SLE had been diagnosed according to the criteria of the American College of Rheumatology (ACR) and prednisone and hydroxychloroquine were started. Prednisone had been tapered and finally stopped after 3 months, and from then on, the patient continued hydroxychloroquine with therapeutic success. Three months before admission, her immunovirological status was good [CD4+ 661 cells/μl, HIV RNA <37 copies/ml] and the patient traveled to her native country where ART was discontinued. Twenty days before admission, the patient returned: her CD4+ count dropped to 247 cells/μl and her HIV RNA rose to 1,044 cp/ml. On the same day, ART was re-started. On admission, laboratory tests showed microcytic anemia, and C-reactive protein (CRP) elevation, electrolyte levels, and creatinine were normal. Urinalysis revealed proteinuria, leucocyturia, and hematuria. CD4+ were 574 cells/μl and HIV RNA<37 copies/ml. Transthoracic echocardiography demonstrated pericardial effusion without tamponade. Empirical antibiotic therapy was administered without improvement. The patients rapidly developed acute renal failure (creatinine 3.25 mg/dl) and nephrotic syndrome (urine protein excretion 7.5 g per 24 h, albumin 1.5 g/dl). Few days later, a generalized vesciculobullous skin eruption was observed. A skin biopsy revealed dermo-epidermal junction dermatitis with focal detachment and granulocytes infiltration. A diagnosis of renal and cutaneous SLE flare was made. Systemic glucocorticoid treatment was started (days 1–3 methylprednisolone 1g/day i.v.; days 4–8 prednisone 50 mg/day po, then prednisone 25 mg/day po) with defervescence, progressive improvement of renal function and resolution of the cutaneous manifestations. The patient was discharged. Two weeks later, cyclophosphamide (0.3 g/m^2 weekly) was added to glucocorticoids. The day after the second administration of cyclophosphamide, a relapse of skin lesions was detected (Fig. 1). The patient

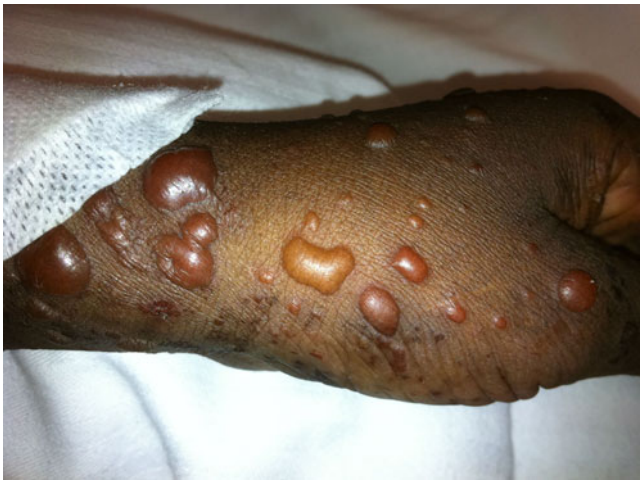

Fig. 1 Cutaneous manifestations of bullous SLE in a HIV-infected woman (case 1)

was readmitted at our hospital. Serology tests pointed out the presence of antinuclear antibodies (ANA) (title 1:640, speckled pattern) and of anti-Smith (Sm) antibodies. A new skin biopsy was performed: it showed huge subepidermal bullous detachment and neutrophilic infiltration. Direct immunofluorescence microscopy revealed deposition of IgG and C3 fraction of complement at the dermal–epidermal junction: these findings were consistent with bullous SLE. High-dose steroid therapy was given (days 1–5 methylprednisolone 125 mg/day intravenously, then prednisone 50 mg/day by mouth). A complete resolution of the lesions was documented and the patient was finally discharged. Despite therapy with cyclophosphamide and kidney function amelioration, high-grade proteinuria still persisted; therefore, with the aim to exclude a HIV-related nephropathy a kidney biopsy was performed. The biopsy showed diffuse thickening of the glomerular basement membrane, as well as subepithelial, subendothelial, and mesangial immune deposits. These findings merited the diagnosis of classes IV–V lupus nephritis according to the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification. Despite 12 cycles of cyclophosphamide (0.3 g/m^2/cycle) and concomitant steroid treatment, proteinuria still persists (4–5 g/day), but CRP is normal as well as C3 and C4 levels and hemoglobin raised from 8 to 12.5 g/L while ESR is stable around 60 mm/h.

Case 2

A 44-year-old Caucasian woman was admitted at Luigi Sacco Hospital because of sudden onset of dysarthria and right hemiparesis. Past medical history revealed multimetameric herpes zoster. On admission, the temperature was 38 °C and the other vital signs were normal. Blood tests revealed anemia (hemoglobin 10.2 g/dl), leukopenia (white blood cells

1,630/μl) and increased erythrocytes sedimentation rate (ESR 102 mm/h). A magnetic resonance of the brain showed a lacunar lesion in the internal left capsule. The patient was started on anticoagulant therapy and several instrumental tests were implemented in order to define the etiology of the lacunar infarct. Transesophageal echocardiography and Doppler ultrasound evaluation of the carotid arteries did not show any pathological findings. No evidence of antiphospholipid antibodies was found. Further evaluations documented the presence of proteinuria (3.2 g/24 h), ANA (titer 1:160, homogeneous pattern), and anti-dsDNA antibodies (titer 1:10). A diagnosis of SLE was made. Since the central nervous system manifestations were not attributable to any other cause than SLE, a SLE-induced vasculitis of the small vessels was considered responsible of the lacunar infarct. Simultaneously HIV1/2 antibodies were detected in the serum of the patient. Because of the advanced stage of HIV infection (CD4+ T cells 60/μl, HIV RNA 62,982 copies/ml), ART (tenofovir/emtricitabine plus lopinavir/ritonavir) was introduced. Two weeks later, laboratory tests documented an initial improvement of the immunovirological status (CD4+ T cells 100/μl, HIV RNA 19,847 copies/ml) and an increased titer of ANA and anti-dsDNA antibodies (1:640 and 1:40, respectively).

Review of the literature

We searched the English medical literature from 1981 to 2012 and we identified 55 patients who received a concomitant diagnosis of SLE and HIV infection [1–43]. The majority of the cases (57.1 %) was recorded in the pre-ART era.

A time relation between HIV infection/diagnosis and SLE manifestations was drawn for 53 patients. SLE diagnosis followed HIV infection in 54.7 % of the cases [1–24]. De novo presentation of SLE after ART introduction was reported in seven patients [6, 8, 9, 11, 14, 18]. On the contrary, SLE became evident before HIV infection and HIV diagnosis in 11.3 % and 30.2 % of the patients, respectively [6, 21, 25–38]. In two patients, SLE and HIV infection were simultaneously diagnosed [39, 40]. Median age at SLE diagnosis was 5.0 years (range 2.5–12.0) in patients who acquired HIV through mother-to-child transmission and 32.0 years (range 23.0–39.0) in patients who acquired HIV through a different route. Six years was the estimated duration of HIV infection before SLE diagnosis. The median CD4+ count at SLE diagnosis was 464 (150–1524) and 353 (214–560) cells/μl in pediatric and adult patients, respectively. Twenty one point one percent of the subjects had a CD4+ count inferior to 200 cells/μl at the time of the first SLE manifestation.

Prevalence of female sex and black race were high in the reported cases (Table 1). Data about HIV risk factors were available for 43 patients: mother-to-child transmission, intravenous drug use, and transplant/transfusion accounted for 25.6 %, 14.0 %, and 11.6 % of the cases, respectively. Heterosexual and homosexual transmission were documented in 39.5 % and 9.3 % of the patients, respectively.

Of the patients, 81.8 % presented at least four of the criteria (median 5.0, range 4.0–6.0) required by the American College of Rheumatology for the diagnosis of SLE. Presence of ANA, immunologic, and hematologic disorders were the commonest findings. An ANA titer ≥1:320 was documented in 86.8 % of the patients. Hypocomplementemia and anti-dsDNA positivity were widespread in the study population (73.0 % and 68.6 %, respectively). Clinical manifestations of SLE varied slightly according with the age of the patients: it is worth noting that malar rash was documented mainly in the adult population (Table 2). Renal disorders were more commonly described in the pediatric population (85.7 % vs. 51.3%; $p=0.05$); proteinuria was documented in 73.5 % of the patients with renal involvement (median value 2.9 g/24 h). A kidney biopsy was performed in 23 subjects: the histopathological results were consistent with lupus nephritis in 91.3 % of the cases (Fig. 2).

Fifty-three patients received treatment for SLE [1–11, 13–18, 20, 22–43]. Hydroxychloroquine, steroids, and immunosuppressive drugs (cyclophosphamide, azathioprine, and mycophenolatemofetil) were administered in 11.3 %, 52.2 %, and 24.5 % of the cases, respectively. Follow-up information were available in 49/55 of the patients [1–8, 10, 12–18, 20–37, 39–41, 43]. An AIDS-related event was the main cause of death for 66.7 % of the 15 patients who died. The vast majority of adverse events were reported in the pre-

Table 1 Demographic data of HIV-infected patients diagnosed with SLE

		Entire population, *n* (%) *n*=55	Pediatric population, *n* (%) *n*=14	Adult population, *n* (%) *n*=39	*p* value (pediatric vs adult population)
Sex	M	18 (32.7)	7 (50.0)	11 (28.2)	0.19
	F	37 (67.3)	7 (50.0)	28 (71.8)	0.19
Race	Asian	1 (2.7)	0 (0.0)	1 (4.0)	1.00
	Black	21 (56.8)	8 (72.7)	13 (52.0)	0.29
	White	15 (40.5)	3 (27.3)	11 (44.0)	0.47
Ethnicity	Hispanic	8 (22.2)	1 (10.0)	6 (24.0)	0.64

Table 2 Fulfillment of the American College of Rheumatology (ACR) criteria for the diagnosis of systemic lupus erythematosus (SLE) in HIV-infected patients

	Entire population, *n* (%) *n*=55	Pediatric population, *n* (%) *n*=14	Adult population, *n* (%) *n*=39	*p* value (pediatric vs adult population)
No. ACR criteria, mean (interquartile range)	5.0 (4.0-6.0)	4.0 (3.0-5.0)	5.0 (4.0-6.0)	0.06
Malar rash	31 (60.8)	3 (30.0)	27 (69.2)	*0.03*
Discoid rash	1 (2.0)	0 (0.0)	1 (2.6)	1.00
Photosensitivity	12 (23.5)	2 (20.0)	10 (25.6)	1.00
Oral ulcers	17 (33.3)	3 (30.0)	14 (35.9)	1.00
Non erosive arthritis	35 (68.6)	7 (70.0)	26 (66.7)	1.00
Pleuritis/pericarditis	16 (31.4)	4 (40.0)	12 (30.8)	0.71
Renal disorders	34 (63.0)	12 (85.7)	20 (51.3)	0.05
Neurologic disorders	6 (12.0)	0 (0.0)	6 (15.4)	0.58
Hematologic disorder	40 (77.0)	9 (81.8)	29 (74.4)	1.00
Immunologic disorder	37 (72.5)	9 (75.0)	27 (73.0)	1.00
Antinuclear antibodies (ANA)	48 (92.3)	12 (92.3)	34 (91.9)	1.00

A two-sided *p* value of <0.05 was considered statistically significant

ART era (10/15). Considering SLE, 75.5 % of the patients experienced an improvement of their rheumatologic disorder. The progression of HIV infection was associated with a remission of SLE in 11 patients [5, 6, 25–27, 30, 33, 34, 37, 38]. A SLE flare was reported after the introduction of HAART in three patients [6, 33, 41]. On the contrary, a severe rebound of HIV RNA was detected in two patients following cyclophosphamide therapy [31, 41].

Discussion

The two cases described and the review of the literature highlight three relevant issues: (1) the rare coexistence of HIV and SLE and their pathogenetic interactions, (2) the multifaceted clinical manifestations of SLE, and (3) the therapeutic challenge posed by the coexistence of SLE and HIV.

1. Coexistence and interactions between SLE and HIV Infection

Fifty-seven cases of SLE in HIV-infected patients have been reported to date. Female to male (2:1) and black to white (1.3:1) ratio in HIV-infected patients differ from the ratios observed in the general population (6:1 and 2:1, respectively). The lower proportion of women can be justified by the less relevant role played by the estrogen hormonal effect due to the high number of pediatric cases in our population.

On one side, the fact that autoimmune diseases can occur despite the loss of immunocompetence caused by HIV seems a paradox. On the other side, the number of cases documented is far below the statistical prediction of Barthel and Wallace [44] even if this number could be underestimated because SLE might be underreported. They suggested that by 1993, there should have been approximately 400 cases in the USA alone, assuming that 500,000 Americans have SLE,

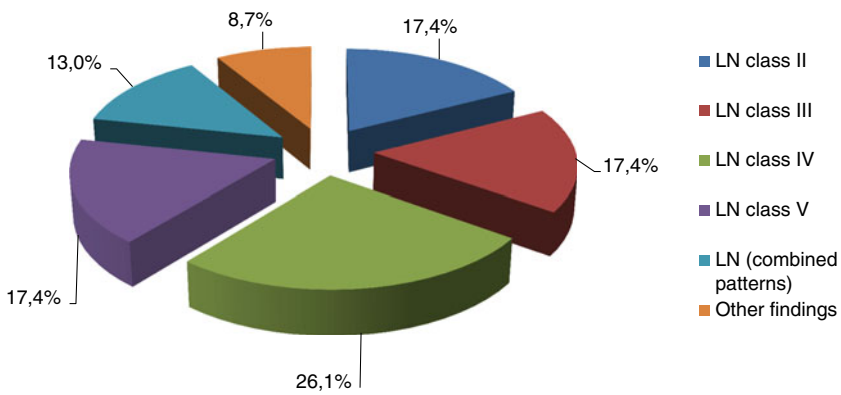

Fig. 2 Kidney biopsy results of HIV positive patients with renal manifestations of systemic lupus

200,000 have AIDS and both diseases are independent and not mutually exclusive. This number could be expected to be higher given the widespread diffusion of HIV infection.

HIV infection is characterized by depletion of regulatory T cells, whose main function is to maintain peripheral self-tolerance and avoid the development of autoimmunity. Furthermore, in 2005, Haynes demonstrated that the two most broadly reactive HIV-1 envelope gp41 human monoclonal antibodies, 2F5 and 4E10, are polyspecific autoantibodies reactive with the phospholipid cardiolipin [45]. If these observations may justify the coexistence of SLE and HIV infection, conversely many others could explain the rarity of this association.

Immunologic factors

First, T CD4+ cells, which are one of the main targets of HIV, play an important role in the pathogenesis of SLE. Anti-dsDNA antibodies, which are instrumental in the pathogenesis of lupus nephritis, are isotype switched and are somatically mutated: these features of antigen driven immune responses are T cell dependent. Moreover, CD4+ T cells interact with multiple autoantigens, support autoantibody production, and promote nephritis. T cells may also be directly active in end organ damage by acting as local mediators of tissue inflammation. There is extensive evidence in animal models of SLE that depletion of T cells is therapeutic and that blocking T–B cells interaction prevents end organ damage. The review of the literature and both our case reports are in line with the above findings in animal models [46]. Eleven patients experienced a remission of SLE manifestation with advanced HIV infection. Four SLE flares and eight de novo presentations of SLE after ART introduction were documented; these events are consistent with immune reconstitution inflammatory syndrome [47]. The privileged position of CD4+ cells in the development of SLE is suggested even by their relatively high count at SLE diagnosis (CD4+ 361 cells/μl). Second, plasmacytoid dendritic cells (pDC) take part to the pathogenesis of SLE. They are potent IFN-producing cells and can activate immature dendritic cells to increase presentation of self-antigens to autoreactive T and B cells. Depletion of IFN-producing pDCs during HIV infection may contribute to the protective effect of HIV against SLE. DCs can be infected by HIV and TLR9 signaling changes in pDC function may be reduced indirectly by HIV gp120. Loss of pDC in HIV infection usually parallels the loss of T CD4+, but the rate of recovery of pDC and CD4+ T cells may be different. The occurrence of SLE after PegIFN α therapy in a HIV/HCV co-infected patient highlights the crucial role played by pDC [22].

Our understanding of the interaction of SLE and HIV infection is still partial and unable to explain some of the biological phenomena encountered in this study. The development of SLE in a patient whose CD4+ count was 0 cells/μl [7] and the improvement of rheumatic manifestations after ART in two subjects [37, 40] suggest that CD4+ cells and pDC are not the only actors in this immunological disease. Finally, it is interesting to note that a SLE diagnosis was reported after HIV infection in 29 patients and before HIV infection in only 6 patients. The reasons for this discrepancy are unclear: epidemiological variables, a protective role of SLE or treatment influences should be considered. In this regard, previous studies demonstrated the ability of hydroxychloroquine to inhibit the post transcriptional production of HIV-1 in monocytes and T cells and also to reduce the residual inflammation in HIV-1 infected patients on effective antiretroviral treatment [48].

Diagnostic factors

The overlapping clinical and laboratory presentation of SLE and HIV may give rise to diagnostic difficulties. As a consequence, many diagnoses can be missed. Active SLE and HIV infection share several manifestations, such as fever, arthralgia, myalgia, lymphoadenopathy, skin rash, cytopenia, and renal involvement. Moreover multiple autoimmune phenomena have been reported in HIV, including the presence of ANA. Thus, distinguishing between HIV and SLE based on autoimmune phenomena may be challenging. Kopelman and Zolla-Pazner described the presence of ANA in 12 % of HIV positive patients without underlying rheumatologic diseases: 89.5 % of these patients had a titer equal to 1:20. On the contrary, in the reported population ANA titer were at least equal to 1:320 in 86.8 % of the patients [31]. Findings of antibodies to double stranded DNA and hypocomplementemia, neither of which is typically seen with HIV infection, might be helpful to ascertain the presence of active SLE: anti-dsDNA and hypocomplementemia were detected in 68.6 % and 73.0 % of the patients included in the analysis. These findings, together with the observation that the ACR requirements were not fulfilled in 10 of the studied patients, are a stimulus to improve the discriminatory power of our diagnostic tools. A revision of the ACR criteria in the setting of HIV population is advisable.

2. Multifaceted clinical manifestations of SLE

The first case reported describes the unique presence of bullous SLE in a HIV-infected patient. Blistering disorders represent a diagnostic challenge since the differential diagnosis is complicated. A wide variety of diseases can result in the formation of blisters on the skin. Autoimmune disorders, drug reactions, infections, genetic disorders, and traumatic injury are among the potential causes of cutaneous blistering. The concomitant flare of lupus nephritis, the generalized distribution of tense, subepidermal blisters, the young age of the patient, and the discontinuation of potentially

involved drugs were useful for narrowing the potential diagnosis. Histological and immunohystochemical findings proved our previous suspicion of bullous SLE. The difficulties in the diagnosis of this rare manifestation of SLE are balanced by an equally difficult treatment strategy. While dapsone is considered the best treatment for patients with isolated bullous SLE, patients with systemic manifestations of lupus not always have an excellent response to the initiation of corticosteroids and immunosuppressors [49]. The neurologic manifestations of the second patient highlight the need for a differential diagnosis between cardiovascular events, HIV-related opportunistic manifestations and autoimmune disorders.

3. Therapeutic challenge posed by the coexistence of SLE and HIV

Efficacy and safety of immune-suppressant treatment for SLE in the context of HIV infection need to be assessed to identify risk factors for HIV disease progression and to evaluate the efficacy of suppressive therapies in controlling the residual immunological activation in HIV-infected patients with suppressed viremia as such immune activation constitutes a persistent trigger for increased cardiovascular disease and metabolic disorders in this group of patients.

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