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CASE REPORT

Immunodeficiency and autoimmunity coming together: a nearly missed diagnosis

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The coexistence of human immunodeficiency virus (HIV) and systemic lupus erythematosus (SLE) appears to be unusual and the prevalence of patients who carry the dual diagnosis is currently unknown. We hereby present a case of a C4 deficient HIV-1 positive Caucasian female under highly active antiretroviral therapy for the past eight years, admitted to hospital with an aggressive and potentially fatal clinical presentation of SLE. There was a favorable outcome despite a significant diagnostic delay. Despite its rarity, the case highlights that this association is remarkable and may be overlooked by clinicians familiar with either condition. *Lupus* (2017) **0,** 1–3.

Key words: Systemic lupus erythematosus; human immunodeficiency virus; highly active antiretroviral therapy

Introduction

Systemic autoimmune diseases may occur in association with primary (1) or secondary (2) immunodeficiency. More specifically, once acquired, human immunodeficiency virus (HIV) infection is thought to ameliorate systemic lupus erythematosus (SLE) (3). We describe an HIV-positive female under antiretroviral therapy with adequate virological control, who presented a diagnostic conundrum, with a rare SLE manifestation and an aggressive clinical course.

Case report

In June 2015, a 50-year-old Caucasian woman with type 1 HIV infection, under abacavir, lamivudine and efavirenz for the past eight years, was admitted under the Infectious Disease Team with a four-week history of fever, productive cough and anorexia. The HIV viral load had been undetectable and the $CD4^+$ T cell count had ranged from 502 to 336/μL from treatment onset. A routine follow-up visit three months previously, found her asymptomatic, with a $CD4^+$ T cell count of 258/μL and an undetectable HIV viral load. One week prior to admission the haemoglobin was 10.9 g/dL, the white cell count was 5700/μL, platelets were 170000/μl and the C-reactive protein 26.7 mg/L (upper limit of normal <5). The chest X-ray was normal and she was empirically started on levofloxacin 500 mg daily but there was no improvement. At admission, she was found to have fever (axillary temperature of 38.4°C) but the rest of the examination was unremarkable. By this time the haemoglobin was 8.7 g/dL, white cell count was 3000/uL, platelets were 129,000/uL, erythrocyte sedimentation rate was 72 mm/h and the C-reactive protein 23.2 mg/L. Once again there were no changes in the chest X-ray, the urinalysis was negative and blood and urine cultures were negative. On day six the chest X-ray showed a right lower lobe consolidation. No structural abnormality was visible by bronchofibroscopy and bronchoalveolar lavage fluid analysis failed to identify *Pneumocystis carinii*, *Mycobacterium tuberculosis* or any other microorganism. At this time, the $CD4^+$ T cell count was 151/μL and the HIV viral load remained undetectable. She was then sequentially treated

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with meropenem and trimethoprim/sulfamethoxazole, with no improvement. After four weeks of hospital admission her condition continued to worsen, she remained febrile and had lost 20 kg (corresponding to 17% of admission body weight). On day 28 she presented with severe dyspnoea and mild haemoptysis. There had been a steady decrease in haemoglobin to 6.5 g/dl, without haemolysis and she received four red cell transfusions (Figure 1a). Chest CT demonstrated bilateral ground glass opacities and a small pleural and pericardial effusion (Figure 1b).

At this time a non-infectious cause for her disease was sought. The anti-nuclear antibody test was positive (titre 1/640), with a homogenous pattern on IF. Several autoantibodies were present (Euroimmun®), namely: anti-dsDNA (135 UI/mL – normal range: <60 UI/mL), anti-Smith (1+), anti-nucleosomes (140.6 U/mL), anti-beta2 glycoprotein1 IgG (21 GPL/mL) and anticardiolipin IgG (16.8 GPL/mL). Lupus anticoagulant was present. Anti-glomerular basement membrane and anti-neutrophilic cytoplasmic antibody tests were negative. Complement C3 was low at 0.19 g/L (0.9–1.8) and complement C4 was undetectable. The 24-hour urine protein was 1940 mg. The renal biopsy revealed class II nephritis according to the International Society of Nephrology/Renal Pathology Society with C1q glomerular and interstitial granular deposits of IgG, IgM, C1q, C3, kappa and lambda chains (Figure 1c, 1d). The diagnosis of systemic lupus erythematosus (SLE) with nephritis and probable alveolar haemorrhage was made. There was a dramatic improvement after she was started on prednisolone (80 mg/day), hydroxychloroquine (HCQ) 400 mg/day and azathioprine (AZA) 100 mg/day. Over the next 12 months the steroids were progressively reduced and discontinued. The anti-dsDNA antibody became undetectable at two months and C3 normalized. At 24 months of follow-up she remains on HCQ and AZA, in SLE remission,

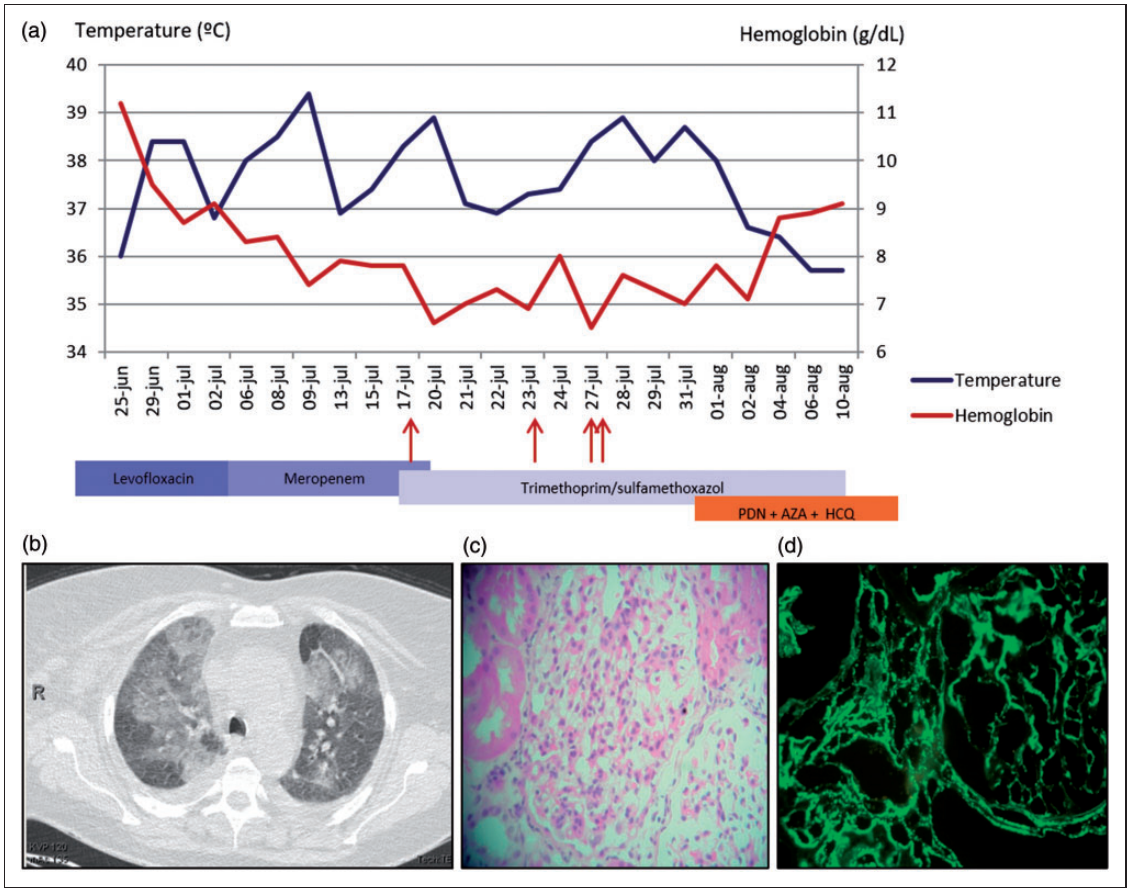

Figure 1 Temperature (blue), haemoglobin (red) and sequential therapies, including red cell concentrate transfusions (arrows) throughout the hospital admission (a); chest CT showing ground glass opacities and pleural and pericardial effusion (b); renal biopsy exhibiting mesangial proliferation (hematoxylin-eosin) (c) and C1q glomerular and interstitial granular deposits (immunofluorescence) (d).

with an undetectable HIV load and a $CD4^+$ T cell count of 473/μL. C4 has remained undetectable throughout the course of disease. There was no family history of autoimmune disease.

Discussion

Fever, weight loss, respiratory symptoms and a low $CD4^+$ T cell count in an HIV-infected individual are often linked to an opportunistic infection. On the other hand, signs of alveolar haemorrhage can often be subtle, with little haemoptysis and the diagnosis is often suspected on the basis of anaemia and chest infiltrates (4,5). Our patient failed to respond to several antibiotics and the diagnosis of alveolar haemorrhage shifted the diagnostic focus to an autoimmune disease.

Several factors may have contributed to SLE onset. She almost certainly has a primary C4 deficiency, in itself associated to SLE (6). Immune dysregulation in the setting of HIV infection itself is associated to autoimmunity (7). Furthermore, restoration of the immune system by highly active antiretroviral therapy (HAART), with the rise of CD4 cells, causes an inflammatory reaction referred to as immune reconstitution inflammatory syndrome (IRIS) (3,8,9). IRIS can result in the unmasking of a previously undiagnosed and untreated condition such as infection or autoimmune disease. Novel SLE or SLE manifestations have been described to occur months or years after HAART, mostly in females and up to the fourth decade of life. Unlike our patient, these have not been described as late as eight years after HIV diagnosis (10). No treatment guidelines for patients with active SLE and HIV infection are available and the efficacy and safety of concomitant use of HAART and immunosuppressive therapy remain to be assessed.

SLE clinical manifestations tend to improve once an individual acquires HIV infection (3). In contrast, our patient had an aggressive and potentially fatal clinical presentation in whom SLE arose in the setting of a primary and a secondary immunodeficiency. The immunological and inflammatory cascade ultimately leading to this association are still poorly understood but the connection between immunodeficiency and autoimmune disease should not be forgotten.

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References

1 Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, members of the CFPIDsg. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. *J Allergy Clin Immunol* 2017.
2 Virot E, Duclos A, Adelaide L, Miailhes P, Hot A, Ferry T, *et al*. Autoimmune diseases and HIV infection: A cross-sectional study. *Medicine (Baltimore)* 2017; 96(4): e5769.
3 Fox RA, Isenberg DA. Human immunodeficiency virus infection in systemic lupus erythematosus. *Arthritis Rheum* 1997; 40(6): 1168–1172.
4 Andrade C, Mendonca T, Farinha F, Correia J, Marinho A, Almeida I, *et al*. Alveolar hemorrhage in systemic lupus erythematosus: A cohort review. *Lupus* 2016; 25(1): 75–80.
5 Mittoo S, Fell CD. Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med* 2014; 35(2): 249–254.
6 Macedo AC, Isaac L. Systemic lupus erythematosus and deficiencies of early components of the complement classical pathway. *Front Immunol* 2016; 7: 55.
7 Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity. *Autoimmun Rev* 2002; 1(6): 329–337.
8 Schneider J, Zatarain E. IRIS and SLE. *Clin Immunol* 2006; 118(2–3): 152–153.
9 Shelburne SA 3rd, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DW, *et al*. Immune reconstitution inflammatory syndrome: Emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)* 2002; 81(3): 213–227.
10 Carugati M, Franzetti M, Torre A, Giorgi R, Genderini A, Strambio de Castilla F, *et al*. Systemic lupus erythematosus and HIV infection: A whimsical relationship. Reports of two cases and review of the literature. *Clin Rheumatol* 2013; 32(9): 1399–1405.