

Systemic Lupus Erythematosus Presenting with Features Suggestive of Human Immunodeficiency Virus Infection

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ABSTRACT. We describe 8 patients who presented with fever, weight loss, anemia, and oral and/or esophageal candidiasis, and who were initially thought to have human immunodeficiency virus (HIV) infection or lymphoma. These patients fulfilled American College of Rheumatology criteria for systemic lupus erythematosus (SLE) because of arthralgias or arthritis, hematological derangements, and immunological abnormalities. Treatment was delayed because SLE did not immediately enter into the differential diagnosis. All patients had a rapid response to corticosteroids, with defervescence of fever, decrease in lymphadenopathy within 24-48 hours, and complete resolution of lymphadenopathy and other signs and symptoms of illness in 7-10 days. It is important to recognize this mode of SLE presentation in patients who test negative for HIV infection so that the appropriate diagnostic evaluation and initiation of treatment can be expedited. (J Rheumatol 2005;32:1365-8)

Key Indexing Terms:

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We describe 8 patients who presented with fever, weight loss, anemia, and oral and/or esophageal candidiasis, and who were initially thought to have human immunodeficiency virus (HIV) infection or lymphoma. These patients fulfilled American College of Rheumatology (ACR) criteria for systemic lupus erythematosus (SLE) because of arthralgias or arthritis, hematological derangements, and immunological abnormalities. Treatment was delayed because SLE did not immediately enter into the differential diagnosis. All patients had a rapid response to corticosteroids, with defervescence of fever, decrease in lymphadenopathy within 24-48 hours, and complete resolution of lymphadenopathy and other signs and symptoms of illness in 7-10 days. It is important to recognize this mode of SLE presentation in patients who test negative for HIV infection so that the appropriate diagnostic evaluation and initiation of treatment can be expedited.

CASE REPORTS

Case 1. A previously healthy 26-year-old woman presented with a 4-month history of fever, malaise, and anorexia with weight loss of 48 lbs, persistent odynophagia, and arthritis involving the wrists, hands, and knees. Review of systems was negative for skin rash, hair loss, photosensitivity, headache, chest or abdominal pain, miscarriage, or Raynaud's phenomenon. Physical examination revealed a cachectic young woman with temperature of 101.9° F. There was thrush involving the hard palate, uvula, posterior pharynx, and buccal mucosa. A non-tender 2 mm oral ulcer was seen on the hard palate. Multiple non-tender lymph nodes, 1 to 3 cm in diameter, were noted in the cervical, axillary, and inguinal regions. The spleen was palpable 3 cm below the left costophrenic margin. The wrists, metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints were tender and swollen.

Laboratory tests revealed a white blood cell count of 2,800/mm³ with 532 lymphocytes and 150 CD4+ T cells/mm³, hemoglobin 5.3 g/dl, and erythrocyte sedimentation rate (ESR) 105 mm/h, ferritin 7,323 ng/ml, LDH 443 U/dl, and haptoglobin 11 mg/dl. Coomb's test was negative and urinalysis was normal. Cultures of blood, sputum, and urine showed no growth. Bone marrow biopsy revealed a hypercellular marrow, stainable iron, and no granulomas, malignant cells, or organisms. Computed tomography (CT) of the abdomen and chest showed splenomegaly and axillary, intrathoracic and intraabdominal lymphadenopathy. Transthoracic echocardiography was normal. Tests for HIV and HTLV-1 by ELISA, polymerase chain reaction (PCR), and Western blot were negative. Subsequent immunological studies revealed antinuclear antibodies (ANA) 1:1280, elevated titers of anti-Sm and anti-DNA antibodies, and decreased serum complement levels.

Methylprednisolone, 32 mg twice daily, was administered intravenously. By the next day marked diminution in size of the lymph nodes and spleen were noted with dramatic improvement of constitutional symptoms, defervescence of fever, and increase in appetite and energy. By day 10 of corticosteroid treatment lymphadenopathy and splenomegaly had completely resolved.

Cases 2-8. The presenting clinical features of 7 other patients are summa-

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rized in Table 1. Most had daily temperature spikes, significant weight loss, oral or esophageal candidiasis, prominent non-tender lymphadenopathy, and peripheral blood lymphopenia. Three patients were Coomb's test positive and 3 others had signs of peripheral red blood cell destruction manifested by high serum LDH and decreased haptoglobin levels, and microovalocytes and/or schistocytes on the peripheral blood smear (Table 2). Serologic abnormalities consistent with SLE were noted in all patients (Table 3). Bone marrow biopsy on 5 patients revealed only hypercellularity. Lymph node biopsies were performed on 4 patients. In Case 5, biopsy revealed prominent follicular hyperplasia with increased vascularity and blood vessels extending into germinal centers with rare onion skinning, increased plasma cells in follicles and interfollicular zones, and focal nuclear debris. Case 2 showed a reactive node with mixed lymphoid cells and numerous plasmacytoid cells. Case 3 showed fibroconnective tissue with acute and chronic inflammation, abscess formation, and granulation tissue, and Case 7 showed lymphadenitis with focal microabscesses.

All patients responded rapidly to corticosteroid therapy at prednisone equivalent doses of 0.5 to 1.5 mg/kg/day, with resolution of fever, appreciable decrease in lymph node size, and loss of malaise within 24 hours. Five patients subsequently developed more typical manifestations of SLE. Case 1 developed Libman-Sachs endocarditis requiring replacement of aortic and mitral valves. Cases 3, 6, and 7 developed central nervous system (CNS) and/or renal disease and required treatment with cyclophosphamide. Case 8 developed vasculitis and CNS disease. Cases 2 and 5 remain well

on hydroxychloroquine and low dose prednisone. One patient, Case 4, was lost to followup after hospital discharge.

DISCUSSION

Although the dominant features of their illness have all been described as occurring in SLE, the presentation of our patients was atypical. With the dominating constitutional symptoms of fever, cachexia, weight loss, oral thrush and/or esophageal candidiasis, and prominent lymphadenopathy with low CD4+ cell counts, the initial diagnosis in these patients was HIV infection or hematologic malignancy. Of note, HIV infected patients can present with lupus-like manifestations such as arthralgias/arthritis, rash, Raynaud's phenomenon, and vasculitis along with positive ANA and other autoantibodies mimicking SLE¹. In most of the patients, the diagnosis of SLE was delayed because it did not immediately enter into their differential diagnosis and the diagnostic serologic tests were not performed as soon as they might have been. While a diagnosis of HIV can now be made rapidly, an earlier diagnosis of SLE would have avoided the

Table 1. Clinical features at initial presentation.

Features	Case							
	1	2	3	4	5	6	7	8
Age	26	30	33	53	23	29	31	32
Ethnicity*	AA	AA	AA	H	AA	A	H	H
Fever, °F	101.7	104.8	103.7	101	106	101.2	103	100.2
Weight loss, lbs	48	NA	20	10	40	26	17	30
Malaise	+	+	+	+	+	+	+	+
Malar rash	-	-	+	-	-	-	-	-
Alopecia	+	-	-	-	-	-	-	-
Oral ulcer	+	-	-	-	-	-	-	-
Arthritis	+	+	+	+	+	+	+	+
Mucosal candidiasis	Oral	-	Oral	Esophageal	-	Oral	Oral	Oral and Esophageal
Lymphadenopathy**	+	+	+	+	+	+	+	+
Splenomegaly	+	-	-	-	-	-	+	-
Serositis	-	-	-	+	-	-	-	-
Renal	-	-	-	-	-	+	-	-
Neuro	-	-	-	-	-	+	-	-

* Ethnicity: AA: African American; H: Hispanic (all from Puerto Rico); A: Asian. ** All documented lymphadenopathy involved nodes that were at least 1 × 1.5 cm.

Table 2. Hematologic findings.

Variable	Case							
	1	2	3	4	5	6	7	8
Hemoglobin	5.3	9.5	6.0	7.7	7.8	8.5	9.5	3.4
Reticulocytes	1.9	0.5	1.6	1.1	0.8	2.8	NA	NA
Lymphs/mm ³	532	567	805	726	510	794	406	700
CD4+/mm ³	150	157	NA	209	158	234	115	211
Coomb's	-	-	+	-	-	-	+	+
Schistocytes	+	-	+	+	-	+	+	+

NA: not available.

Table 3. Immunologic findings.

Variable	Case							
	1	2	3	4	5	6	7	8
HIV	-	-	-	-	-	-	-	-
ANA	> 1:1280	1:640	1:1280	1:1280	1:1280	> 1:1280	1:640	2+
Anti-dsDNA (normal range)	> 200 (< 34)	708 (< 423)	> 200 (< 34)	657 (< 423)	789 (< 423)	1144 (< 423)	1109 (< 70)	2.7 (< 0.5)
C3 (mg/dl) (normal range)	42 (50–160)	< 28 (70–245)	< 52 (50–160)	53 (50–160)	39 (50–160)	< 50 (50–160)	103 (50–160)	NA*
C4 (mg/dl) (normal range)	13.7 (5–35)	< 5.6 (16–56)	< 7 (5–35)	10.4 (5–35)	NA	NA	7.8 (16–56)	NA
Anti-Sm	+	-	+	-	NA	-	+	NA
Anti-Ro	+	-	-	-	NA	+	-	NA
Anti-La	-	-	+	-	NA	+	-	NA
Anti-RNP	+	+	+	+	NA	-	+	+
Anti-cardiolipin IgG (normal < 20)	27.3	-	22.7	-	-	20.6	-	-
IgM	-	-	-	-	-	-	-	-

* Not available. CH50 was 115 (normal > 150) in Case 8.

need for lymph node biopsy in several of our patients. Despite the unusual disease presentation, these patients fulfilled ACR criteria for the diagnosis of SLE and most subsequently developed other SLE manifestations including CNS and renal disease.

Lymphadenopathy is relatively uncommon at initial presentation of SLE²⁻⁴, and only 2-6% of SLE patients have hemolytic anemia when they first present⁴. Presentation with lymphadenopathy has been reported in a single series⁵ of 21 SLE patients, 16 of whom were febrile, 12 leukopenic, and 8 anemic (3 Coomb's test positive) whereas only 6 had rash, 4 had serositis, and other manifestations classical for SLE were absent.

The finding of oral and/or esophageal candidiasis in 6 of our 8 patients was most striking. To our knowledge, candida infection has not previously been described as an initial presenting manifestation of SLE in the absence of immunosuppressive therapy. The seemingly paradoxical occurrence of an opportunistic infection generally associated with immunodeficiency in patients with an autoimmune disorder may be related to their peripheral blood CD4 lymphopenia since protection from candida infection relies on type 1 cell-mediated immunity^{6,7}. It is possible that peripheral lymphopenia in the presence of enlarged lymph nodes may be a manifestation of activation induced cell death.

In spite of the prominence of lymphadenopathy in our patients, lymph node biopsy was of limited diagnostic usefulness with findings ranging from reactive hyperplasia to necrotizing lymphadenitis. Necrotizing lymphadenitis, can be diagnostic of SLE when hematoxylin bodies and plasma cells are present⁸. In addition, lymph node biopsy may be useful in excluding Castleman's disease characterized by vascular proliferation in germinal centers, and Kikuchi disease where plasma cell infiltration is rare, both of which can

present with clinical manifestations similar to those of our patients^{8,9}.

The rapid and dramatic response of our patients to corticosteroid therapy at dose levels equivalent to 0.5 to 1.5 mg/kg/day of prednisone, with defervescence of fever and decrease in adenopathy noted in 24-48 hours, suggests that cytokines may have played an important role in producing their disease manifestations, in contrast to antibody-mediated manifestations such as glomerulonephritis or cerebritis, which take considerably longer to improve with treatment. Serum levels of interleukin (IL)-6 and interferon- γ (INF- γ) have been found to be elevated in SLE patients with lymphadenopathy^{10,11}. IL-6 in particular can cause fever, anorexia, fatigue, and weight loss¹⁰. Transgenic mice that overexpress IL-6 have marked lymphadenopathy, splenomegaly, and altered T cell populations¹². Glucocorticoids are known to block the transcription of mRNA for a variety of cytokines including IL-6, tumor necrosis factor- α , and INF- γ ^{13,14}, and the half-life of cytokine activity *in vivo* is far shorter than that of antibodies.

In conclusion, we have identified a distinct subset of patients with SLE who present with marked lymphadenopathy, weight loss, candida infection, lymphopenia with low CD4+ T cell count, and hemolytic anemia, in whom diagnosis was delayed due to the absence of classical manifestations of SLE. The uniformly rapid response to corticosteroid treatment may shed light on the underlying mechanism of this distinct expression of immune dysregulation.

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