Disseminated Histoplasmosis in Systemic Lupus Erythematosus: Case Report and Review of the Literature

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Objectives: **To report a patient who developed both central nervous system systemic lupus erythematosus (SLE) and disseminated histoplasmosis and to review the literature regarding histoplasma infection in patients with SLE.**
Methods: **MEDLINE review of the medical literature published in English.**
Results: **Disseminated histoplasmosis occurs rarely in patients with SLE. The main risk factor is treatment with corticosteroids at doses of 20 mg/d or greater. Fever, dyspnea, pleurisy, and weight loss are typical presenting symptoms. The most commonly involved tissues are lung, liver, and bone marrow. In our patient, both SLE flare and disseminated histoplasmosis were present simultaneously.**
Conclusions: **Opportunistic infection is an important complication of SLE and may be difficult to diagnose. Symptoms of infection may mimic those of a lupus flare, or conversely, symptoms may be masked by the use of corticosteroids. Fever, unexplained tissue involvement, atypical clinical patterns, and poor response to immunosuppressive therapy should alert the clinician to aggressively pursue evaluation of possible infection in patients with SLE.**
Semin Arthritis Rheum 28:193-199. ***Copyright © 1998 by W.B. Saunders Company***

INDEX WORDS: Systemic lupus erythematosus; fungal infection; opportunistic infection; histoplasmosis; *Histoplasma capsulatum.*

WE PRESENT a case of a woman with systemic lupus erythematosus (SLE) who developed confusion and hepatitis. Her illness defied Occam's razor by having two separate causes—infection and lupus flare. Differentiating between infection and a lupus flare can be difficult. This patient had central nervous system (CNS) disease caused by SLE and hepatitis, pancytopenia, and fever from disseminated histoplasmosis. Individuals with SLE are predisposed to infection by virtue of inherent immunologic defects as well as treatment with immunosuppressive medication (1). In this article, we review the previously published cases of SLE and disseminated histoplasmosis and discuss the difficulties in diagnosing infection in patients with SLE, the risk factors for infection, and the potential interactions between infection and SLE flare. We briefly review liver involvement in SLE and discuss how our patient's liver disease differs from that of SLE-related hepatitis.

CASE REPORT

A 53-year-old African American woman presented to Duke University Medical Center (DUMC) in June 1997 with confusion and hepatitis. She was diagnosed with SLE 10 years before this date based on the presence of arthralgia, fatigue, serum antinuclear antibodies (1:2560 titer, speckled pattern), anti-Sm and ribonucleoprotein (RNP) antibodies, and low complement levels. She had a pulmonary hemorrhage in January 1996 that was attributed to SLE and responded well to high doses of prednisone.

In January 1997, she noted worsening fatigue, which interfered with her occupation as a secretary. Her rheumatologist found no evidence of anemia, kidney dysfunction, or liver disease, and the patient was treated with 30 mg prednisone per day, with

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0049-0172/98/2803-0006$8.00/0

minimal improvement in symptoms. She traveled to Alabama in May, where she developed an upper respiratory tract infection with fever and malaise. She returned from her trip with increasing fatigue, generalized weakness, and impaired concentration. A physician treated the patient with fluoxetine for possible depression, but this medication was stopped after the patient developed dizziness.

Over the next month, she reported difficulty with remembering to take her medications. Kidney, liver and thyroid function tests, and a chest radiograph were normal. A magnetic resonance imaging scan of the brain also was normal. A second trial of prednisone at 80 mg/day produced no clinical improvement. One week before her initial evaluation at DUMC, she developed difficulty walking and was evaluated by a neurologist. Cerebrospinal fluid from a lumbar puncture was normal with no pleocytosis, increased protein, or oligoclonal bands. An electroencephalogram showed generalized slowing. One day before admission, the patient's husband noted yellow discoloration of her eyes. She was evaluated at a local hospital and found to have icterus, oral thrush, and diffuse weakness with an inability to lift her legs off the bed. She was oriented only to person and place. Laboratory studies showed pancytopenia and markedly elevated liver function tests. She was then transferred to DUMC for further evaluation.

When admitted to DUMC, the patient was alert but confused. Her history was negative for ingestion of drugs, including aspirin and related products, acetaminophen, and alcohol. She had received a blood transfusion in January 1996 during the episode of pulmonary hemorrhage. She denied other symptoms of active SLE, including joint pain, new rash, oral ulcers, pleurisy, hair loss, Raynaud's phenomenon, or sicca symptoms.

Physical examination showed a disoriented woman with a temperature of 38°C, scleral icterus, and oral thrush. No organomegaly or asterixis was present. Laboratory studies were remarkable for pancytopenia and elevated liver function tests (Table 1). Antiplatelet antibodies were also elevated. Coombs' test, complement levels, and double-stranded DNA antibodies were normal or negative. Blood smear showed no schistocytes. Tests for cytomegalovirus, Epstein-Barr virus, hepatitis A, B, and C, and human immunodeficiency virus were negative. Results of a repeat lumbar puncture were normal, including negative Gram stain, India ink preparation, cryptococcal antigen, and bacterial

Table 1: Laboratory Studies Throughout Hospital Course

Laboratory Studies	Hospital Day 1	Hospital Day 8	Hospital Day 19	Hospital Day 44
White blood cell count ($\times 10^9$)	2.5	3.1	0.7	4.2
Hematocrit (%)	0.29	0.27	0.28	0.27
Platelet count ($\times 10^9$)	50	140	91	296
Creatinine (mg/dL)	0.6	0.5	0.5	0.6
AST (U/L)	1,212	542	125	39
ALT (U/L)	502	311	118	40
Alkaline phosphatase (U/L)	1,331	1,346	1,389	943
Total bilirubin (mg/dL)	7.3	7.1	3.8	1.5
GGT (U/L)	5,777			
Urinalysis	1+ Protein, 12 WBC, 6 RBC, +nitrite, 5–50 bacteria	Normal		
Westergren sedimentation rate (mm/h)	85			
Protime, partial thromboplastin time	Normal			

NOTE. Normal values: white cell count, 3.2–9.8 $\times 10^9$ blood; hematocrit, 0.35–0.45; platelets, 15–450 $\times 10^9$ blood; creatinine, 0.7–1.4 mg/dL; AST, 10–60 U/L; ALT, 10–60 U/L; alkaline phosphatase, 30–135 U/L; total bilirubin, 0.2–1.2 mg/dL; GGT, 8–55 U/L; Westergren sedimentation rate, 0–15 mm/h.

Abbreviations: AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transaminase; WBC, white blood cells; RBC, red blood cells.

and viral cultures. Because of normal cerebrospinal fluid studies, the microbiology laboratory did not perform special stains or cultures for fungi and tuberculosis. Serum antimitochondrial, anti-ribosomal P, and antineuronal antibodies were negative.

Brain magnetic resonance imaging was repeated at DUMC and was normal. An abdominal computed tomography scan showed multiple simple liver cysts but was otherwise unremarkable. An electroencephalogram showed diffuse symmetric slowing with triphasic spikes in the frontal region.

The patient was thought to have CNS involvement secondary to SLE. She was treated initially with intravenous antibiotics until blood cultures returned negative at 72 hours. Intravenous methylprednisolone was given on the fifth hospital day at 1 mg/kg/d in divided doses. Later that day, the patient developed a tonic-clonic seizure and was treated with phenytoin. The patient's mental status improved over the next 2 to 3 days, but then worsened again, with increasing agitation and confusion.

A liver biopsy was performed that showed features of chronic active hepatitis, mild nonsuppurative cholangitis, and poorly formed granulomas consistent with primary biliary cirrhosis or an autoimmune hepatitis. Special stains for iron, Epstein-Barr virus, herpes simplex virus, tuberculosis, and fungal elements were all negative. Liver enzymes decreased by approximately 50%, but were still markedly abnormal. She also had persistent pancytopenia. A bone marrow biopsy was performed that showed normal cellularity, noncaseating granulomas, and negative staining for fungal and acid-fast organisms.

Intravenous cyclophosphamide was given on hospital day 14 at a dose of 750 mg/m^2 because of persistent fever and altered mental status attributed to SLE. Her mental status improved over the next several days, but the patient continued to have fever to 40°C. The white blood cell count dropped to 700 cells/mm^3 5 days after receiving cyclophosphamide with 540 neutrophils/mm^3 (hospital day 19). A urinary tract infection was treated with antibiotics, but fever persisted.

On hospital day 25, the bone marrow culture was reported to be growing *Histoplasma capsulatum.* Subsequent testing for urine histoplasma antigen was positive. The patient was treated with amphotericin B at a dosage of 0.7 mg/kg/d for 14 days, followed by a 6-month course of itraconazole. After several days of antifungal therapy, the patient's fever, blood counts, and liver enzymes improved. She was discharged home in good condition with a normal mental status.

METHODS

We reviewed the literature describing patients with SLE who develop disseminated histoplasmosis to define the clinical presentation of infection, risk factors for infection, coexistence of SLE flare, and clinical outcome. To our knowledge, there has been no other review of this subject since the 1970s. A search of the English-language literature using MEDLINE from January 1966 to February 1998 identified papers for this review. Search terms included *SLE, fungal infection, opportunistic infection,* and *Histoplasma capsulatum.* We reviewed the reference lists of all articles obtained to identify additional articles.

RESULTS

A total of eight cases of SLE and histoplasma infection were identified. Seven of these cases had adequate data describing symptoms, method of diagnosis, treatment, and clinical outcome and were included in this review. These seven cases are summarized in Table 2. All patients had disseminated histoplasmosis and five were women. Common presenting symptoms were fever, dyspnea or pleurisy, and weight loss (six, four, and three patients, respectively). Lung, liver, and bone marrow were the most commonly involved tissues. Six of seven patients were taking prednisone at a minimum dose of 20 mg daily, two were taking 6-mercaptopurine, and one was taking azathioprine. Diagnosis was delayed in two of the three patients for whom this information was mentioned. Death occurred in four of the seven patients.

In two patients, there was clinical or autopsy evidence of SLE flare. In the first case, the patient had a positive Coomb's test and polyserositis on autopsy that was attributed to SLE (2). This patient also had *Candida* pneumonia, which could have contributed to his serositis. In the second case, the patient had arthralgia, myalgia, Coombs'-positive hemolytic anemia, and concomitant histoplasma infection. Her initial tests for antinuclear and DNA antibodies were negative, but the test for serum

Table 2: Features of Patients With SLE and Disseminated Histoplasmosis

Reference	Age (yr), Gender	Immunosuppressive Medication	Symptoms	Examination Findings	Tissues Involved	SLE Flare	Antifungal Treatment	Outcome
2	49, W	Prednisone 20 mg/d	Dyspnea, cough, sputum, pleurisy, night sweats, weight loss	Fever, mild hepatosplenomegaly	Lung, liver, spleen, bone marrow, kidney, lymph node, intestine	Yes	Amp B	D
3	22, W	High-dose steroids, azathioprine	Fever, change in vision	NS	Bone marrow, liver, spleen, eye	NS	Amp B	D
4	23, W	Prednisone 40 mg/d	Fever, night sweats, lethargy, pleurisy	Palpable liver edge	Lung, liver, bone marrow	No	Amp B	S
5	65, M	High-dose steroids, 6-mercaptopurine	Fever, fatigue, dyspnea	NS	Lung, liver, spleen, bone marrow, kidney	NS	Amp B	D
5	23, W	High-dose steroids	Fever, malaise, weight loss	NS	Lung, liver, bone marrow	NS	Amp B	S
5	35, M	High-dose steroids, 6-mercaptopurine	Fever, malaise, weight loss, dyspnea	NS	Lung, kidney, brain	NS	None	D
6	56, W	None	Fever, rash, headache, myalgia, arthralgia	Cervical adenopathy, papular skin rash	Skin, lung	Yes	Amp B, fluoro	S
Our case	53, W	Prednisone 80 mg/d	Fever, confusion, fatigue, weakness, jaundice	Fever, icterus, two papulaes	Bone marrow, liver	Yes	Amp B, itra	S

Abbreviations: W, woman; M, man; NS, not stated; Amp B, Amphotericin B; fluoro, fluorocytesine; itra, itraconazole; D, died; S, survived.

antinuclear antibody became positive 9 months later leading to the diagnosis of SLE (6).

In summary, most patients with SLE and disseminated histoplasmosis were receiving immunosuppressive medication, which would predispose to opportunistic infection. Death occurred in more than half of this group, indicating a poor outcome for patients with SLE who develop disseminated histoplasmosis. Diagnosis of histoplasmosis was delayed in at least two patients. There was some evidence of SLE disease activity in two patients at the time of infection, although in one case a diagnosis of SLE could not be made until 9 months later, and in the other case the serositis may have been attributable to a complicating infection. Thus, our patient is similar to others in the literature, with concomitant use of immunosuppressive medication and delay in diagnosis. Distinguishing features in our case included markedly elevated liver function tests, absence of pulmonary involvement, and presence of SLE flare. We were fortunate that bone marrow culture grew *H capsulatum,* allowing for

successful treatment of infection and an excellent clinical outcome.

DISCUSSION

Prevalence and Risk Factors for Infection in SLE

Since the 1950s, infection has been a leading cause of death in SLE, accounting for 21% to 50% of fatalities (1). In a multicenter study performed in the 1980s, infection was the cause of death in 33%, and active SLE caused death in 31% (7). Opportunistic infections are common and in one study were present in 53% of 19 patients with SLE taking high-dose steroids and cytotoxic drugs over a period of several weeks (8). The leading opportunistic infections included *Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans, Nocardia asteroides,* and *Pneumocystis carinii* (1, 4, 8, 12). Although histoplasmosis is endemic to the Mississippi and Ohio River valleys, disseminated histoplasmosis is less commonly reported in SLE than these other opportunistic organisms.

A retrospective review of 44 deaths in SLE patients showed that 55% had an infection during their terminal hospitalization (9). Ten of these deaths were attributed to opportunistic infection, and only one patient was diagnosed accurately before autopsy. High prednisone dose and cytotoxic drug therapy in the 3 months before admission were strong risk factors for fatal infection. Delay in diagnosis of opportunistic infection was attributed to several factors. First, symptoms of infection mimicked those of active SLE, and the presence of active lupus in one organ system led to a failure to consider the diagnosis of infection in another organ system. In addition, delay in appropriate workup and false-negative test results (such as negative open lung biopsy in two patients with disseminated aspergillosis) also contributed to the low rate of antemortem diagnosis of infection.

Ginzler and colleagues prospectively studied 223 patients with SLE to determine the risk factors for infection (10). Over a 3-year period, 384 infections occurred in 150 patients, and 28 infections (7%) were described as opportunistic. High-dose corticosteroid therapy was the greatest risk factor for infection. Lupus nephritis and SLE flare were also risk factors, although the criteria for lupus activity were not provided. When corrected for steroid dose, active urinary sediment remained a significant risk factor for infection. The rate of all infections was fivefold higher, and the rate of opportunistic infection was 42-fold higher in patients taking more than 40 mg prednisone daily, compared with patients not taking corticosteroids.

In a multicenter study by Rosner et al, infection was a contributing factor in 44% of all deaths of SLE patients (7). High-dose corticosteroid therapy was a risk factor for infection in this series. SLE activity was noted in 58% of those with infection as the primary cause of death. The most frequent coexisting disease manifestations of SLE were nephritis and CNS involvement.

Immunologic defects occur in SLE and are well described in a recent review (1). These abnormalities appear to be independent of the use of immunosuppressive medications. In a study evaluating the risk of infection in patients with SLE and rheumatoid arthritis, those with SLE had a higher infection rate than individuals with rheumatoid arthritis taking the same doses of corticosteroids (12). Several immunologic defects have been associated with SLE and include impaired phagocytosis by macrophages, decreased neutrophil number and function, decreased cytokine production, decreased natural killer cell numbers, low complement levels, and functional asplenia (1). Decreased production of the cytokines interferon-γ, interleukins 1, 2, and 10, and tumor necrosis factor alpha have all been demonstrated (1). Of particular interest is that some immune defects are more pronounced during SLE flares, including lymphopenia, T cell helper dysfunction, low numbers of natural killer cells, and low complement levels (1).

Cell-Mediated Immunity and Histoplasma Infection

Studies in mouse models of histoplasmosis substantiate the importance of cell-mediated immunity in controlling infection. Anti–IL-12 antibody given to mice infected with *Histoplasma* increased the fungal burden and led to 100% mortality (13). The same mice also had lower levels of interferon-γ, a key cytokine in cell-mediated immunity. In another study, mice depleted of CD4 cells died within 2 weeks of injection with sublethal doses of *Histoplasma,* and depletion of CD8 cells resulted in higher fungal burden, compared with control mice (14). Treatment of *Histoplasma*-infected mice with anti-tumor necrosis factor alpha antibody resulted

in increased mortality and increased fungal burden (15). Thus, cell-mediated immunity is critical for control of *Histoplasma* infection. Because cell-mediated immunity may be impaired in SLE, deficiencies in this arm of the immune system may play a role in predisposing these patients to opportunistic infection.

Interaction Between Infection and Lupus Activity

The interaction between infection and lupus activity may be understood in part by a model of allostatic load (11). Theoretically, allostatic systems allow the body to adapt to stress, and an inadequate response in one system can trigger compensatory responses in another system. In patients receiving long-term corticosteroid therapy, for example, adrenal insufficiency could lead to an inadequate cortisol response to infection. To compensate, another system might augment cytokine production and result in increased SLE activity.

In our patient, we speculate that *Histoplasma* infection could have triggered a flare of SLE. Conversely, use of high-dose steroids for CNS lupus may have led to increased susceptibility to infection, and the patient acquired *Histoplasma* infection during her trip to Alabama.

SLE and Hepatitis

Liver involvement in SLE is an unusual but recognized occurrence. More commonly, liver disease in patients with SLE is associated with use of nonsteroidal antiinflammatory drugs and other medications, infections, and toxins. Notably, only 5 of 77 cases of unexplained hepatitis in patients with SLE had liver biopsy specimens in which the histopathology showed granulomas (16-22). Markedly elevated liver function tests, such as occurred in our case, have been described in only three previous case reports. In one study, hepatitis correlated with other indices of increased lupus activity (20), whereas another study showed that all six patients with SLE and hepatitis had antiribosomal P antibodies (19). Although the presence of hepatic granulomas in our patient could have been due to SLE, it was an important clue to the presence of fungal infection. The strikingly elevated serum transaminases in our patient were most likely due to histoplasmosis.

CONCLUSIONS

We present a patient with SLE who had fever, confusion, markedly elevated liver enzymes, and pancytopenia. Although infection was suspected, it was not evident during the initial evaluation. The patient was treated for CNS SLE, leading to improvement in mental status but persistence of fever, abnormal liver enzymes and cytopenias. Bone marrow culture grew *Histoplasma capsulatum* on hospital day 25, and the patient returned to normal after treatment with amphotericin B.

We believe the CNS manifestations of our patient were due to SLE rather than to CNS histoplasmosis or hepatic encephalopathy. The minimally elevated serum ammonia levels, absence of asterixis, and findings on electroencephalogram made hepatic encephalopathy less likely. CNS histoplasmosis would be expected to cause symptoms and signs of meningitis, elevated CSF white cells, and worsening of mental status after treatment with systemic immunosuppressive therapy.

This case illustrates several points. Opportunistic infection remains an important complication of SLE and may be difficult to recognize in patients with a concomitant SLE flare. For example, symptoms of infection such as fever, skin rash, and pleurisy may mimic those of active lupus. Corticosteroid therapy also can mask symptoms of infection. These factors may lead to a delay in diagnosis of infection. Clinicians should be alert to the possibility of opportunistic infection in patients with SLE flare and aggressively pursue potential infectious causes in cases characterized by fever, unexplained tissue involvement, atypical clinical patterns, or poor response to immunosuppressive therapy.

ACKNOWLEDGMENT

We thank Dr David Pisetsky for his thoughtful review of the manuscript.

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