Markedly Elevated Serum Lactate Dehydrogenase Levels Are a Clue to the Diagnosis of Disseminated Histoplasmosis in Patients with AIDS

Gavin R. Corcoran,* Hail Al-Abdely, Christopher D. Flanders, Jone Geimer, and Thomas F. Patterson

Disseminated histoplasmosis is a common late manifestation of AIDS, but the diagnosis may be unsuspected in some patients because the clinical presentation of histoplasmosis may mimic other opportunistic infections. High serum lactate dehydrogenase (LDH) levels have been associated with disseminated histoplasmosis. We therefore evaluated whether markedly increased LDH levels were useful for making a diagnosis of disseminated histoplasmosis by comparing admission LDH levels for 15 patients with culture-proven disseminated histoplasmosis with those for 30 patients with advanced AIDS who were admitted to the hospital for evaluation of pulmonary infiltrates and fever. The mean admission LDH level in patients with disseminated histoplasmosis was 1,356 IU/L (range, 145–5,410 IU) whereas it was 332 (range, 77–832 IU) in the patients with other pulmonary processes. Admission LDH levels were >600 IU in 11 (73%) of the 15 patients with disseminated histoplasmosis vs. 3 (10%) of controls ($P < .001$). We conclude that markedly elevated admission LDH levels may be a clinical clue to the diagnosis of disseminated histoplasmosis in patients with AIDS.

Now that patients with HIV infection are surviving longer, disseminated mycobacterial and fungal infections have become more frequent late manifestations of AIDS [1, 2]. The diagnosis of these disseminated infectious complications of late-stage HIV infection may be difficult because the clinical presentation is frequently nonspecific. Important historical clues such as local endemic infections (e.g., histoplasmosis or coccidioidomycosis) may be helpful in narrowing the differential diagnosis.

Diagnostic tests including cultures of blood and bone marrow and measurement of Histoplasma antigen in serum or urine are useful in establishing a diagnosis of histoplasmosis in patients with AIDS [3, 4]; however, histoplasmosis may not be considered prominently in the differential diagnosis of a disseminated infection, particularly in regions of the country where histoplasmosis is relatively uncommon. Thus, the diagnosis of histoplasmosis may be delayed in these regions.

Disseminated histoplasmosis can mimic a variety of more common opportunistic infections such as Pneumocystis carinii pneumonia (PCP), tuberculosis, and Mycobacterium avium complex infection; therefore, a high index of suspicion is needed to establish the diagnosis of this disease. A delay in the diagnosis and failure to institute appropriate therapy may lead to increased mortality [5, 6].

Early diagnostic clues would be valuable for making the clinical diagnosis of disseminated histoplasmosis. High lactate dehydrogenase (LDH) levels have been associated with a variety of conditions including septic shock, lymphoma and other malignancies, and tissue infarction or hypoxia [7]. In addition, elevated LDH levels have been reported in patients with granulomatous diseases including disseminated histoplasmosis [8], tuberculosis [9], and pulmonary toxoplasmosis [10].

The acute clinical presentations and rapidly fatal courses of two patients with disseminated histoplasmosis prompted us to review these patients’ records for early clinical clues that may have suggested the diagnosis of disseminated histoplasmosis on presentation. Admission LDH levels were >2,000 IU/L in both patients. To evaluate markedly elevated LDH levels as early clinical clues to the diagnosis of histoplasmosis, we reviewed the records of all HIV-infected patients with disseminated histoplasmosis who were admitted to our institution over a 1-year period, and we compared these data with those for patients with advanced AIDS who were admitted to an HIV Inpatient service for evaluation of pulmonary infiltrates and fever.

Methods

Disseminated histoplasmosis was defined as a positive culture of either blood or bone marrow, as determined with the BACTEC system (Becton Dickinson, Cockeysville, MD) or Isolator (Merck, Darmstadt, Germany) blood culture system. On the basis of this definition, we reviewed the records of the Mycology Laboratory at the University Hospital and at the South Texas Veterans’ Health Care System, Andie L. Murphy
Division, San Antonio, for a 1-year period to identify all patients with cultures positive for *Histoplasma capsulatum* (All patients with positive blood or bone marrow cultures were infected with HIV.) We then reviewed the medical records of these patients for the initial clinical presentations and serum laboratory values. We recorded admission and peak LDH values. Serum LDH levels were measured in International Units (IU) with use of a colorimetric assay (Paramax, Model 720ZX; Dade, Santa Ana, CA). Standard reference values for both men and women were 80–180 IU/L.

Patients admitted to the HIV Inpatient service at the University Hospital over 3 months during the period selected for the patients with histoplasmosis served as controls. Inclusion criteria for controls were a CD4 cell count of <200/mm³, the presence of pulmonary infiltrates, and a temperature of >38°C. For all controls, cultures of blood and sputum were negative for *H. capsulatum*. Admission LDH levels and CD4 cell counts at presentation for the 15 patients with disseminated histoplasmosis were compared with those for the 30 patients with pulmonary infiltrates who did not have histoplasmosis. The data were analyzed by using Epi-Info Version 6.0 (Centers for Disease Control and Prevention).

**Results**

We identified 15 patients who were admitted to our center over a 1-year period with a diagnosis of disseminated histoplasmosis and AIDS. All 15 patients had blood cultures positive for *H. capsulatum*. Two patients also had positive respiratory samples; four had documented extrapulmonary sites of infection (bone marrow, three patients; colon, one). The mean (± SE) number of days between admission and the diagnosis of histoplasmosis was 21.2 ± 2.6 days (range, 8–42 days).

The control group consisted of 30 consecutive HIV-infected patients admitted to the HIV Inpatient service over a 3-month period during that same year for evaluation of pulmonary infiltrates and fever. The mean CD4 cell count for the study group was 25/mm³ (range, 1–82/mm³), and that for the control group was 41/mm³ (range, 0–184/mm³) (*P* > .05). The principal admission diagnoses for the controls included PCP (either proven or presumed) (19 patients [63%]), bacterial pneumonia (eight [27%]), and mycobacterial infections (three [10%]).

The ranges of LDH levels in the two groups are shown in figure 1. The mean admission LDH level was 1,356 IU/L (range, 145–5,410 IU) in the study group and 332 IU (range, 77–832 IU) in the patients without histoplasmosis (*P* > .05). The principal admission diagnoses for the controls included PCP (either proven or presumed) (19 patients [63%]), bacterial pneumonia (eight [27%]), and mycobacterial infections (three [10%]).

The ranges of LDH levels in the two groups are shown in figure 1. The mean admission LDH level was 1,356 IU/L (range, 145–5,410 IU) in the study group and 332 IU (range, 77–832 IU) in the patients without histoplasmosis (*P* < .03). LDH levels were increased above the upper limit of normal (>180 IU/L) in 14 (93%) of 15 patients with disseminated histoplasmosis and in 26 (87%) of 30 controls (*P* > .05). We used an arbitrary LDH level of 600 IU/L (more than three times the upper limit of normal) to suggest a diagnosis of histoplasmosis. We found that 11 (73%) of the 15 patients with disseminated histoplasmosis had admission LDH levels of >600 IU, whereas only 3 (10%) of the 30 controls had admission LDH levels of >600 IU (figure 1) (*P* < .001). When the two groups were compared on the basis of these markedly increased LDH levels, the odds ratio of having disseminated histoplasmosis was 24.75 (exact 95% CI, 3.84–197; *P* < .001).

Increased mortality was associated with high LDH levels in patients who had disseminated histoplasmosis. The mean LDH level for the patients with disseminated histoplasmosis who died during the current hospitalization was 2,071 IU/L, whereas it was 730 for those who survived (*P* < .05). Three (60%) of five patients with LDH levels of >1,000 died, while three (30%) of 10 patients with LDH levels of <1,000 IU/L died (figure 1). No patient in the group without disseminated histoplasmosis had LDH levels of >1,000.

**Discussion**

At our institution, as at others located in areas where histoplasmosis is endemic or occurs in patients with reactivated
infection [6], disseminated histoplasmosis should be strongly considered in the differential diagnosis for patients with markedly elevated admission serum LDH levels and late-stage HIV infection. Even in areas where histoplasmosis is not endemic, a markedly elevated LDH level in an HIV-infected patient may be an important clinical clue to the diagnosis of disseminated histoplasmosis because an elevated LDH level may reflect reactivation of disease acquired while the patient was living in an area where H. capsulatum is endemic [1, 2]. On the other hand, in areas where the fungus is not endemic, other conditions, including disseminated tuberculosis [9] and lymphoma, may result in high LDH levels.

Patients with other more-common opportunistic infections, such as PCP, also have increased levels of LDH [9]. A diagnosis of PCP may frequently be assumed for patients with AIDS who present with pulmonary infiltrates and fever, and other diagnoses may not be considered. We arbitrarily chose an admission LDH level of 600 IU/L because it is three times the upper limit of normal. An LDH level of >600 IU should not be considered diagnostic; it should instead suggest that a diagnosis other than PCP or bacterial pneumonia be considered. In the study by Quist and Hill [9], even the patients with PCP seldom had LDH levels of >1,000 IU/L [9]. In our study, five (33%) of 15 patients with histoplasmosis had LDH levels of >1,000 IU/L, whereas none of the 30 patients with other pulmonary conditions had such high levels of LDH.

Other conditions including septic shock and tissue hypoxia or infarction and other infections such as pulmonary toxoplasmosis and disseminated tuberculosis have been associated with markedly elevated LDH values [7, 9, 10]. A sepsis-like syndrome associated with disseminated intravascular coagulation and a high mortality rate has been described for patients with disseminated histoplasmosis and AIDS [1, 2]. None of the patients with disseminated histoplasmosis in this report were hypotensive or had an admission diagnosis of sepsis. However, the mortality during hospitalization was 60% among patients with LDH levels of >1,000 IU/L; this finding suggests that markedly elevated LDH levels may warrant more aggressive therapy, such as that with empirical high-dose amphotericin B, in this clinical setting [2, 6, 11].

Urine and serum Histoplasma antigen levels have been shown to correlate with the extent of disease [4, 5]. Unfortunately, Histoplasma antigen levels were not routinely measured for our patients; therefore, we could not correlate LDH levels with antigen levels, and the diagnoses were delayed for a mean period of ~3 weeks after admission. The relevance of obtaining serial LDH levels for determining the response to therapy could not be assessed with respect to our patients. However, the increased mortality associated with high LDH levels suggests a possible role for LDH-level measurement in the management of disseminated histoplasmosis. In addition, we did not assess the source of the excess LDH in our patients because we did not measure LDH isoenzyme levels. The relevance of serial LDH measurements for the management of infection or for assessing the risk of relapse is an interesting question and deserves further study.

In conclusion, we found that markedly increased LDH levels (>600 IU/L) were significantly more likely to occur in HIV-infected patients with disseminated histoplasmosis than in patients with pulmonary infiltrates and fever that mimicked the presentation of disseminated histoplasmosis. An increased LDH level may be a useful clinical clue to the diagnosis of disseminated histoplasmosis.

References