Fever and high lactate dehydrogenase in HIV-positive patients from the Antilles and Surinam: histoplasmosis?

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ABSTRACT

We describe four cases of HIV-positive patients, two from Surinam, one from the Dutch Antilles and one from Nigeria, who presented with a febrile illness and a high lactate dehydrogenase plasma level. In all four, the diagnosis of disseminated histoplasmosis was made, in three of them by liver biopsy. Two patients had retinal abnormalities compatible with a systemic fungal infection. Three patients were treated successfully with antifungal agents. One patient died. Between 2000 and 2006, only 14 patients with HIV have been found to have histoplasmosis in the Netherlands. Although histoplasmosis is not endemic in the Netherlands, physicians are more likely to see cases because of a growing number of HIV-positive immigrants from endemic regions.

KEYWORDS

Histoplasma, HIV, lactate dehydrogenase

INTRODUCTION

Although disseminated histoplasmosis is a common AIDS-defining condition in endemic countries, it is rarely encountered in Northwest Europe. In the Netherlands, histoplasmosis was diagnosed in 14 HIV-positive patients from January 2000 to January 2006 (data from the HIV Monitoring Foundation). Only one patient was born in the Netherlands. The other patients originated from Western Africa (3) and Southern and Central America (8). Since physicians from Western Europe may not be familiar with this life-threatening disease, there may be a fatal delay in diagnosis. In this article, we describe four patients, all of whom had high plasma lactate dehydrogenase (LDH) levels. LDH might be used to decide about the treatment of histoplasmosis empirically before definite identification of the organism is available.

CASE REPORT 1

A 41-year-old Negroid man from Surinam with a two-year history of HIV infection presented with pain in the upper abdomen and fever for a couple of days. Physical examination did not reveal any abnormalities. Laboratory results showed panleukopenia (1.5 x 109/l), normocytic anaemia (5.0 mmol/l), thrombopenia (88 x 109/l), erythrocyte sedimentation rate (ESR) 135 mm/h, aspartate aminotransferase (ASAT) 50 U/l, alanine aminotransferase (ALAT) 20 U/l, LDH 1413 U/l, and CD4 count 8/mm3. Microbiological examination commonly used in HIV patients to find the origin of fever remained negative. On bone marrow examination granulomatous lesions were found without any micro-organisms. The patient was first treated with tuberculostatic drugs without effect on the fever. Finally, histoplasmosis was found in a liver biopsy (figure 1). He was treated with amphotericin B, followed by itraconazole 200 mg twice daily for four years. The fever resolved within three days. He finally died four years later of other complications of his HIV infection.

CASE REPORT 2

A 54-year-old Negroid woman from Curacao was admitted from another hospital for treatment of progressive renal insufficiency with proteinuria and a coincidentally
diagnosed HIV infection. She had a six-year history of diabetes mellitus and had experienced an episode of erythema multiforme of unknown aetiology after a visit to Curacao, four years prior to her admission. She had not returned to Curacao after that last visit. She complained of episodes of fever, fatigue and frontal headache for a few months. She had a systolic ejection murmur. There was no stiffness of the neck. White retinal lesions were seen on fundoscopy. Leucocytes were $5.0 \times 10^9/l$ with lymphopenia ($0.6 \times 10^9/l$), microcytic anaemia ($6.4 \text{ mmol/l}$), thrombocytes $288 \times 10^9/l$, ESR $95 \text{ mm/h}$, creatinine $1100 \text{ µmol/l}$, urea $32 \text{ mmol/l}$, total protein $47 \text{ g/l}$, albumin $14 \text{ g/l}$, ASAT $176 \text{ U/l}$, ALAT $59 \text{ U/l}$, LDH $3715 \text{ U/l}$, $\gamma$-glutamyltransferase, $141 \text{ U/l}$, CD4 count $6/\text{mm}^3$, HIV-RNA $>10^6 \text{ copies/ml}$, and urinary protein $15 \text{ g/24h}$. Standard microbiological and mycobacterial cultures remained negative. Radiological examination with ultrasound and computed tomography (CT) scan showed pleural effusion, enlarged liver, enlarged echogenic kidneys, few iliacal lymph nodes and some ascites. Kidney biopsy revealed HIV-associated nephropathy. Finally, histoplasmosis could be diagnosed from liver biopsy, performed one week after admission. The patient was treated with itraconazole $200 \text{ mg twice daily}$, but died two days later of multiple organ failure. At autopsy histoplasmosis was found in most of her organs.

CASE REPORT 3

A 26-year-old Negroid Surinam HIV-positive male, who had been in the Netherlands for one year, was admitted because of fever for two weeks, $10 \text{ kg}$ weight loss and loss of vision of his left eye. On physical examination an oral Candida infection, a skin ulcer on the chin and a palpable liver were found. A white exudate and a retinal detachment were seen at fundoscopy. Leucocytes were $3.6 \times 10^9/l$ with a left shift. Haemoglobin was $6.5 \text{ mmol/l}$, thrombocytes $151 \times 10^9/l$, creatinine $113 \text{ µmol/l}$, ASAT $242 \text{ U/l}$, ALAT $50 \text{ U/l}$, LDH $3100 \text{ U/l}$, CD4 count $12/\text{mm}^3$, and HIV-RNA $>10^6 \text{ copies/ml}$. Standard examination of blood, faeces and pleural fluid did not yield any micro-organisms. Viral culture of the chin ulcer revealed a herpes simplex type 2 infection. Mild spleen and liver enlargement was seen at ultrasound. The patient refused a liver biopsy. Based on earlier experience, disseminated histoplasmosis was suspected. Amphotericin B was started five days after admission, followed by itraconazole. No antibodies against Histoplasma could be detected with an immunodiffusion test. The fever receded and the LDH normalised within two days. Blood cultures grew Histoplasma capsulatum 13 days after admission. He was treated with antiviral combination therapy and continued itraconazole. Within three months, CD4 cells rose to $170/\text{mm}^3$ and HIV-RNA became undetectable. Six months later he was readmitted with extensive cutaneous histoplasmosis after he had stopped all medication.

CASE REPORT 4

A Negroid man from Nigeria had resided in the Netherlands for 3.5 years. He had a history of malaria (Plasmodium vivax) and presented with fever and chills after a root canal treatment at the dentist. He reported weight loss of $15 \text{ kg}$ in the previous months. On physical examination he had a systolic cardiac murmur at the apex. No abnormalities were found at fundoscopy. A HIV test was positive. Leucocytes were $3.9$ with $3.4 \text{ granulocytes and } 0.5 \times 10^9/l$ mononuclear cells. Haemoglobin was $5.3 \text{ mmol/l}$ with a mean cellular volume of $81 \text{ fl}$, thrombocytes $237 \times 10^9/l$, ESR $128 \text{ mm}$, C-reactive protein $40 \text{ U/l}$, creatinine $92 \text{ µmol/l}$, ASAT $67 \text{ U/l}$, ALAT $28 \text{ U/l}$, LDH $1516 \text{ U/l}$, and...
LDH iso-enzymes: lactate dehydrogenase 1 iso-enzyme (LD1) 270, LD2 347, LD3 312, LD4 174, and LD5 162 U/l. The CD4 count was 14/mm³ and HIV-RNA >10⁶ copies/ml. Initial standard microbiological and mycobacterial cultures remained negative. *Histoplasma* serology was negative. Reticulonodular lesions were seen on plain chest X-ray. CT scan of the neck, thorax and abdomen showed alveolar infiltrates, mediastinal lymphadenopathy and an enlarged spleen (14 cm). Bone marrow aspiration revealed HIV myelopathy and foamy histiocytes with micro-organisms resembling *Histoplasma*, intense iron staining and sideroblasts. Lung, liver and cervical lymph node biopsy all showed *Histoplasma*. Treatment with amphotericin B was started two weeks after admission. One week later, blood cultures grew *Histoplasma*. The fever receded in six days, and he recovered fully. Nine months later, he was in excellent condition on antiviral therapy and itroconazole. His CD4 cells were 370/mm³ and HIV RNA was undetectable.

**DISCUSSION**

*Histoplasmosis capsulatum* is a dimorphic organism. The hyphae or conidia of the organism are inhaled and can reach the alveoli, where they can germinate at 37°C into the yeast phase and invade the body.³ In tissue, these yeast cells are found in the macrophages as small buds. The acute infection is mostly asymptomatic, but can present as a flu-like illness, with pulmonary symptoms, skin lesions, pericarditis or rheumatological manifestations. The infection can be cured or develop into a chronic pulmonary disease mimicking tuberculosis. In patients with an immunodeficiency or in those who encounter a high inoculum, *Histoplasma* may spread throughout the body via the reticulo-endothelial system, and cause disseminated histoplasmosis infecting nearly all the organs.³ The organs most often involved are liver, spleen, lymph nodes, bone marrow, adrenal glands, gastrointestinal tract and central nervous system.³,⁴ As with mycobacteria, the organism can stay viable in calcified lesions. These dormant organisms can reactivate and in some cases cause systemic disease in case of waning immunity. T-cell immunity plays a paramount role in the activity of the human defence system against *Histoplasma*. T-cells and cytokines such as interleukin (IL)-12, tumour necrosis factor α (TNF-α) and interferon-γ trigger macrophages to kill intracellular *Histoplasma*.³

Endemic areas for *Histoplasma* are the mid-west of the USA, the Caribbean, Central America, Africa and other tropical parts of the world.⁴ The Netherlands is not a reservoir. In HIV infection, systemic infection may either be caused by exogenous exposure in endemic regions, or in nonendemic areas such as the Netherlands, by reactivation of latent infection. In nonendemic areas, clusters of cases of infection are sometimes caused by micro-foci of *Histoplasma*.⁶,⁷ With the increasing number of immigrants from Africa and the (former) Dutch colonies in the Caribbean and Surinam, Dutch physicians are more likely to encounter cases of histoplasmosis. Data from the HIV Monitoring Foundation show that in the Netherlands all patients with histoplasmosis except one originated from endemic areas, pointing to reactivation of infection secondary to severe immunodeficiency.

The diagnosis of disseminated histoplasmosis requires knowledge of the various often nonspecific modes of presentation. Common symptoms and signs are fever (92-95%), weight loss (63-95%), diarrhoea (50%), pneumonitis (50%), lymphadenopathy (20%) and hepatosplenomegaly (25-42%).³,⁸ Less commonly occurring symptoms are gastrointestinal, skin, mucosal and central nervous system abnormalities. Keys to diagnosis are laboratory findings suggesting multiorgan involvement, blood cultures (positive in 85%), chest X-ray (interstitial or reticulonodular infiltrates with or without mediastinal adenopathy in 45-70%) and cerebral fluid examination.⁵,⁹,¹⁰ Bone marrow infection is suggested by anaemia, leucopenia and thrombocytopenia. Pancytopenia is present in 35% of cases, and cultures of bone marrow are positive in over 75%. Liver involvement is often accompanied by serum elevations of transferases (48%), alkaline phosphatase, bilirubin and LDH. Because the fatality rate is high in disseminated histoplasmosis in HIV infection, prompt diagnosis is of great importance. Blood cultures yield a sensitivity as high as 85% with AIDS.³⁹ However, the organism grows very slowly, as was the case in our patients. An easy method is to detect antigen or antibodies against the capsule of the fungus in urine or blood.³⁰-³⁴ Sensitivity during an outbreak in Indiana was reported to be 92% for antigen tests and 71% for serology. For both the antigen and serological tests, cross-reactivity with other fungal infections hampers its use. Besides, the antibodies are often absent in case of severe immunodeficiency. The sensitivity for the antigen test is higher in urine than in serum and is especially useful in monitoring the progress of therapy.⁵

Especially LDH is a useful tool in diagnosis. In a study by Corcoran and coworkers, AIDS patients with disseminated histoplasmosis were found to have an average LDH of 1356 IU/l compared with 332 IU/l in patients with other pulmonary processes. LDH levels were more than 600 IU/l in 73% of patients with disseminated histoplasmosis compared with 10% of controls (p<0.001).³⁵ A descriptive study of patients in an endemic area found elevated LDH levels of >3 times the normal level in 74% of patients.³ Other studies have also identified a high LDH as a positive predictor for histoplasmosis, especially if there are differential diagnostic problems with mycobacterial disease and *Pneumocystis pneumonia*.³⁶,³⁷
Furthermore, a high LDH is associated with a fatal outcome in disseminated histoplasmosis.\(^7\) The high enzyme levels might have their origin in the bone marrow where they are formed in a process called haemophagocytosis or the reactive haemophagocytic syndrome.\(^7\) One study indeed found an association between high serum LDH levels and bone marrow stain positivity for histoplasmosis.\(^6\) Haemophagocytosis is due to inappropriate monocyte activation associated with a number of infections, immune diseases and malignancies. Its characteristics are high fever, anaemia, coagulation disorders, hypotension, liver dysfunction and systemic proliferation of mature histiocytes showing haemophagocytosis. Microscopically, histiocytes can be seen with an abundant load of intracytoplasmic Histoplasma and phagocytosed normoblasts. The incidence in disseminated histoplasmosis has been observed to be as high as \(67\%\).\(^7\) To our knowledge, no research has been done on the predominant isoforms of the high LDH levels. In case report 4, the LDH isoenzymes were measured by electrophoresis. All iso-enzymes seemed to be elevated in the patient's serum, with the elevation of LD\(_2\) (H\(_2\)M\(_2\) tetramere type) being most pronounced. The chemical patterns of the iso-enzymes are therefore nonspecific, but resemble those in mononucleosis, myeloid leukaemia, carcinomatosis and pancreatitis. Further research is needed to the origin of the LDH. Possible aetiological processes include liver damage, haemophagocytosis and general tissue destruction by massive dissemination.

Histology is of highest importance to the diagnosis. In tissue samples, typical intracellular budding yeast can be observed within the macrophages with a periodic acid Schiff (PAS) or Grocott stain. The liver is almost always infected, making it a good target organ for biopsy.

Untreated, acute disseminated histoplasmosis in immunosuppressed patients is fatal.\(^7\) With treatment, the mortality can be decreased to less than 25\%.\(^9\) The Guidelines of the Infectious Disease Society of America-Mycoses Study Group (IDSA-MSG) might well be considered the gold standard for treatment.\(^10\) Therapy is divided into a 12-week induction phase and, in case of immunodeficiency, a lifelong maintenance phase to prevent relapse. A recent study suggested that maintenance therapy might be safely discontinued after successful treatment with highly active anti-retroviral therapy (HAART).\(^9\) Due to the small number of studied subjects, the IDSA still advises lifelong prophylaxis to prevent relapse. Amphotericin B is recommended for induction, followed by itraconazole 200 mg twice daily when possible. As an alternative, itraconazole can be given to less ill patients. Fluconazole, though less efficacious, is an alternative for patients intolerant to itraconazole. Recently, posaconazole was suggested as a rescue treatment modality after its efficacy against histoplasmosis had been proven in animal models.\(^11\) Another promising but even less studied agent is voriconazole.

Many investigators, for instance the Swiss HIV Cohort Study Group and the HIV Outpatient Study Investigators (USA), have demonstrated a decrease in AIDS-related diagnoses with HAART.\(^11\) However, to our knowledge, large studies on the effect of HAART on the prevalence and treatment of disseminated histoplasmosis are not available. Since disseminated histoplasmosis usually occurs with a CD\(_4\) count of less than 100, the use of potent antiretroviral therapy is likely to decrease the incidence of disseminated histoplasmosis.

**CONCLUSION**

In Northwest European HIV patients originating from the Antilles, Surinam and other endemic areas, fever and a high LDH should raise suspicion of disseminated histoplasmosis, especially in the presence of retinal fungal infection. Liver biopsy has a high diagnostic yield. LDH might be used to treat histoplasmosis empirically before definite identification of the organism is available. Between 2000 and 2006, only 14 patients with HIV were diagnosed with histoplasmosis in the Netherlands. Disseminated histoplasmosis is a treatable HIV complication if recognised and treated early and has an excellent prognosis with antiviral treatment and secondary itraconazole prophylaxis. The low incidence and growing number of patients at risk make a higher awareness of the disease and its symptoms in nonendemic areas critically important.

**REFERENCES**


