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Disseminated histoplasmosis in AIDS: a case report

Wei-Bin Liang, Yuan-Ti Lee, Chun-Ming Lee

Department of Internal Medicine, Mackay Memorial Hospital

Abstract

A 30-year-old aboriginal man previously in good health was admitted because of persistent abdominal pain for 6 days and generalized lymphadenopathy over half a year. Panendoscope showed gastric ulcer and duodenal ulcer. Biopsies of stomach revealed fungal infection and helicobacter pylori (HP) infection in the ulcer. Abdominal computed tomography (CT) showed hepatosplenomegaly, lymphadenopathy in the periaortic area and bilateral inguinal area. Aspiration cytology from neck lymphadenopathy revealed fungal infection with histoplasmosis capsulatum. Blood culture grew Aspergillus niger. On the fourth hospital day, the patient suffered from septic shock, acute renal failure and respiratory failure. Amphotericin B 50 mg daily was given. The patient failed to respond to antimicrobial therapy and died on the fifth hospital day.

Key words : AIDS, disseminated histoplasmosis, lymphadenopathy hepatomegaly, splenomegaly, histoplasma capsulatum, amphotericin B

Introduction :

Histoplasmosis is the most common systemic mycosis and a major cause of morbidity in patients who live in endemic areas. It is worldwide in distribution but more prevalent in certain parts of North and Latin America [1]. Human infection has a number of different clinical pictures, including acute pulmonary histoplasmosis (the most common form), chronic pulmonary histoplasmosis and disseminated histoplasmosis[2,3].

Disseminated histoplasmosis is rare and occurs in one in 2000 infecions with underlying immunosuppressive conditions, including those receiving

chemotherapy, AIDS sufferers, the elderly and infants with immature immunity.

Other chronic diseases such as diabetes, renal failure, cirrhosis and splenectomy may also predispose to dissemination [4,5,2,3]. We reported disseminated histoplasmosis in an AIDS patient with lymphadenopathy, hepatosplenomegaly, body weight loss and peritonitis.

Case report :

A 30-year-old aboriginal man who had been suffering from diffused abdominal pain for 6 days came to our emergency room for help. The patient was single and denied any history of parenteral drug abuse, homosexual behavior, or blood transfusion. He was a laborer. 12 years previously, he had been a sailor for 2 years. On arrival, his temperature was 36.8 °C, he had heart beat 144 per minute, respiratory rate was 20 / min,and blood pressure was 105 / 68 mmHg. Physical examination showed diffuse abdominal tenderness and hard, fixed, painless enlarged lymph nodes over left neck(two, 3×2 cm), left shoulder(five, 1×1 cm), left subaxillary(one, 2×2 cm), right subaxillary(one, 2×2 cm), left inguinal(two, 1×1 cm) and right inguinal(three, 1×1 cm) areas. The patient did not smoke, but drank alcohol and had an operation history of appendectomy 20 years ago. Chest roentgenogram and radiography of the abdomen showed negative finding [figure 1]. Laboratory data revealed Hb 11.0 gm/dl, Ht 33.0 %, WBC 8600 / mm^3, platelet 34000 / mm^3, Glucose 125 mg / dl, BUN 43 mg / dl, Cr 1.3 mg / dl, Na 128 mmol / l, K 5.0 mmol / l, Cl 93 mmol /l, amylase 16 u/l, GoT 22 u/l. We consulted the surgeon; no emergency laparotomy indication was considered. Next day at ER, the patient still complained of diffuse abdominal pain. The vital signs were stable. Due to the persistence of the abdominal pain, abdominal echogram and panendoscope were performed. Abdominal echogram showed compatibility with alcoholic liver disease with early cirrhosis change, splenomegaly, gallbladder polyp and minimal ascites. Panendoscope showed multiple nodules with ulcers over the antrum and body of stomach and an ulcer over anterior wall of duodenal bulb; biopsies were done . Abdominal CT revealed hepatosplenomegaly, confluent lymphadenopathy in the periaortic area and bilateral inguinal areas, diffuse infiltration in the subcutaneous tissue and mesentery area, and fluid accumulation in the peritoneal cavity [figure 2]. Significant laboratory data revealed Hb 9.1 gm / dl, Ht 27.8 %, WBC 8370 / mm^3, BUN 48 mg / dl, Cr 1.6 mg / dl. Human immunodeficiency virus(HIV) antibody was also checked. Surgeon was consulted again, no emergency surgical condition was suggested, and malignant disease was suspected. He was admitted to the internal medicine ward under the impression of lymphadenopathy and suspicion of malignancy and peritonitis.

On the second hospital day, the vital signs were stable. Diffuse abdominal pain was still noted. Laboratory data revealed Hb 10 gm / dl, Ht 29.7 %, WBC 10010 / mm^3, platelet 10000 / mm^3, prothrombin time (PT) 10.5 sec, partial thromboplastin time (APTT) 34.2 sec, ESR 62 sec, glucose 121 mg / dl, total protein 5.2 g /dl, albumin 1.3 g / dl, BUN 54 mg / dl, Cr 1.9 mg / dl. We thought that lymphoma was the most possible etiology. On the third hospital day, the vital signs were stable, but abdominal pain persisted. Laboratory data revealed Hb 10 gm / dl, Ht 30.0 %, WBC 15890 / mm^3, platelet 95000 / mm^3, PT 12.1 sec, APTT 34.2 sec. We evaluated the following possibility of lymph node enlargement and management: (1) Tuberculosis- we gave rifampicin and streptomycin. (2) Scrub typhus- we gave doxycycline and check tsutsugamuchi antibody. (3) Lymphoma- lymph node biopsy. We also checked anti-EBV VCA IgG; IgM; IgA, anti-EBV EA IgG, anti-EBV NA IgG, CMV IgG; IgM, Q fever and widal test; they all showed negative. Empirical antibiotics were also given, and blood culture was checked for suspicion of sepsis. Unfortunately, in the afternoon of the same day, laboratory data revealed BUN 71 gm / dl, Cr 4.0 gm / dl. Later, dyspnea was noted. Lower blood pressure was also measured. Chest roentgenogram showed right pleural effusion [figure 3].Room air arterial blood gas revealed PH 7.416, PaCO2 22.2 mmHg, PaO2 86.0 mmHg, $HCO3^-$ 14.0 meq / l, BE – 10.6 meq / l. Due to the patient's critical condition, he was transferred to ICU for further care under the impression of septic shock, acute renal failure and suspicion of lymphoma and tuberculosis. The next day, after transferring to ICU, the patient began to lose consciousness. Systolic blood pressure was about 90 to 100 mmHg or lower;it became impossible to measure. Arterial blood gas consistently showed metabolic acidosis. Laboratory data revealed Hb 6.3 gm/dl, Ht 19.9 %, WBC 21966 / mm^3, BUN 77 gm / dl, Cr 4.2 gm / dl, K 6.7 mmol / l. Serology of HIV was positive. CD4/CD8 ratio was 1.3/38.2 and the CD4+ T cell count was 76/uL (some days later, the western blot test also showed positive).Stomach biopsy showed fungus infection and helicobacter pylori infection in the ulcer. Periodic acid-Schiff (PAS) stain revealed positive staining of the fungus and discernable capsule formation of a yeast-like microorganism [figure 4]. Amphotericin B was therefore given for fungal infection. Due to poor respiratory pattern, tachycardia, poor arterial blood gas and cyanosis with cold limbs, intubation was performed. Lymph node aspiration from neck for smear and cytology was done; it showed fungal infection with histoplasmosis capsulatum. The patient failed to respond to antimicrobial therapy, and died due to septic shock, disseminated histoplasmosis, AIDS, and peritonitis on the fifth hospital day.

Discussion

Defective cellular immunity associated with AIDS may place the

infected person at risk for a variety of opportunistic infections such as histoplasmosis. Because of the limited geographic distribution, the percentage of AIDS cases in the United States with histoplasmosis is only approximately 0.5%. The median CD4+ T cell count for patients with histoplasmosis was 33/uL in one study.

Histoplasma capsulatum is a dimorphic fungus, the yeast form of which parasitises mammalian macrophage[2]. Histoplasma capsulatum is found in “ microfoci ”, such as bird roosts, caves, chicken coops and environmental sites with large numbers of birds. According to the statement of our patient, he was not exposed to any of the possible infection sources that described above. Infection with Histoplasma capsulatum results if conidia are inhaled into the lungs. The micro- and macroconidia germinate into yeast-like forms that incite the influx of neutrophils, macrophages and fungicidal potintial. Within a few days, specific anti-Histoplasma capsulatum antibodies appear, further enhancing the fungicidal capacities of natural killer cells by antibody-dependent cytotoxicity. Some 2 to 3 weeks after exposure, specific T-cell immunity develops in association with macrophage activated to fungicidal capability[3,6]. These defense mechanisms control the infection in immunocompetent individuals, explaining the subclinical or self-limited course characteristic of acute histoplasmosis. Progressive illness highlighted by hematogenous dissemination occurs in persons with impaired cellular immunity[4]. Recovery from histoplasmosis confers partial immunity against reinfection.

In clinical manifestation of disseminated histoplasmosis, they are nonspecific[3,7]. Unexplained fever and weight loss are the usual complaints. Hepatomagaly, splenomegaly or lymphadenopathy are found in one-third to two-thirds of cases and, less frequently, adrenal, central nervous system, skin or mucosal lesions, or chronic meningitis[3,7,8]. Chest roentgenograms are abnormal in 70 %, showing mediastinal adenopathy in 20 %, miliary infiltrates in 10 to 20 %, and diffuse reticulonodular infiltrates in 20 %[6]. Pleural effusion and thickening occur infrequently in cases of histoplasmosis[9]. Our case presented with body weight loss, lymphadenopathy, hepatosplenomegaly, peritonitis, right pleural effusion, sepsis, anemia and thrombocytopenia. Laboratory findings of anemia, leukopenia and thrombocytopenia suggest bone marrow involvement. Elevation of the alkaline phosphatase level suggests hepatic involvement[6].

In diagnosis, culture, fungal stains, antigen detection, and serological tests for antibodies are useful[10,11]. The sensitivities of disseminated histoplasmosis diagnosis for culture, stain, antigen and serology are 85%, 43 %, 92 %, and 71 %, respectively. For culture in disseminated histoplasmosis, Histoplasma capsulatum may be isolated from blood in 50% to 70 %, bone marrow in 70 % to 80 %, lung in 70 %, liver in 33 % and urine in 30 % of cases. Sputum cultures are positive in 60 % of the cases of

cavitary histoplasmosis[3,6,12,13]. In stain, Hematoxylin-eosin or Gomori Methenamine silver stains of biopsy material provide rapid diagnostic clues but are positive in only 50 % to 70 % of patients with disseminated infection. In relation to particular tissues, the rates of positivety are: lungs, 80 % to 90 %; bone marrow, 50 %; and liver, 29 %[3,6,12,13]. Serology includes immunodiffusion (ID) test for H or M bands, complement fixation (CF) titers, and radioimmunoassay (RIA) and enzyme-linked immunosorbent assay (ELISA) for IgM and IgG antibodies. The ID test is less sensitive and becomes positive later than the CF test. RIA and ELISA have potential for identifying patients with early infections (less than 4 weeks after exposure) as well as for distinguishing recent (IgM- and IgG- positive) from remote (IgG-positive , IgM-negative) infection, but they are less specific than CF and ID[3,6,12,13]. In antigen, the detection of a glycoprotein antigen by RIA in the urine, blood, bronchoalveolar lavage liquid, and CSF is a valuable method. It is useful for following the response to treatment and identifying relapses[3,6,12,13].

Histoplasmin skin tests are not useful diagnostically because of false positive results in patients with other fungal diseases, false negative results in half of patients with disseminated disease, and high background rates of skin test positivity (50 % to 80 %) in endemic areas. The only role for skin testing is in epidemiologic studies of the prevalence of histoplasmosis[6,12,13].

Abdominal computed tomography in patients with disseminated histoplasmosis may disclose hepatomegaly, splenomegaly, diffuse splenic hypoattenuation, adrenal enlargement, extensive mesenteric or retroperitoneal lymphadenopathy, or thickening of the omentum with linear strands and nodular densities of the mesentery. Central, low-density intraabdominal lymph nodes were shown in 33 % of 16 patients undergoing abdominal CT. Such CT findings are not specific, and can be seen in AIDS patients who have disseminated mycobacterial infection with intraabdominal lymphadenopathy. Therefore, definitive diagnosis depends upon the demonstration of Histoplasma capsulatum in the lymph nodes or other tissues[14].

Diagnosis requires recognition of the clinical syndrome, a high index of suspicion, and knowledge of the accuracy and limitations of tests used for the diagnosis of fungal infection.Our patient was diagnosed with histoplasmosis by tissue biopsy (stomach and lymph node) and fungal stain.

Treatment is indicated in all patients with disseminated histoplasmosis. The mortality of untreated disseminated histoplasmosis is 80 %[8], but this can be

reduced to less than 25 % with antifungal therapy[7,15,16,17].
Amphotericin B induces a more rapid response than does itraconazole[18], supporting its selection for more severe cases. Patients with disseminated histoplasmosis, including those with AIDS, usually respond to amphotericin B within 2 to 7 days, providing a useful clue to the diagnosis. A typical course of treatment with amphotericin B (35 mg or more / Kg, given over 8 to 12 weeks) is curative in more than 90 % of cases[12,13]. Itraconazole (200 mg tid for a loading dose, then 200 mg bid) is used to prevent relapse after completion of amphotericin B therapy in AIDS patients with histoplasmosis. However, ketoconazole should not be used in patients who are immunosuppressed[19,21]. During the second week of therapy with ketoconazole and itracoanzole, blood levels should be measured (2 to 4 hours after a dose). Concentration of at least 2 ug / ml should be regarded as therapeutic. Dosage may be reduced in patients with levels above 10 ug/ml[18,19,20,21]. Fluconazole dosage for disseminated histoplasmosis in patients with AIDS should be 800 mg daily, while lower doses may be adequate in other cases. The duration of ketoconazole, itraconazole and fluconazole therapy is unknown, but probably should be at least 12 months for disseminated histoplasmosis. ESR and Histoplasma capsulatum antigen levels should be normal before stopping therapy[18,19,20,21].

Our patient was diagnosed with disseminated histoplasmosis in 5 days after coming to our hospital and being treated with amphotericin B, but he still expired due to being immunocompromised with severe sepsis. In summary, disseminated histoplasmosis may be acute and severe, so it should always be kept in mind that early diagnosis and early treatment are important.

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後天免疫功能不全症候群併發組織漿菌病的個案報告

梁衛賓　　李原地　　李聰明

馬偕醫院　內科

摘　　要

一位 30 歲的原住民男性，之前健康良好。這次因持續性的肚子痛 6 天和全身性的淋巴腺腫大超過半年而入院。胃鏡發現胃潰瘍和十二指腸潰瘍。胃部切片顯示潰瘍中有黴菌和幽門螺旋桿菌感染。腹部電腦斷層顯示肝脾腫大和位於主動脈旁與雙側鼠蹊部的淋巴腺腫大。頸部淋巴腺穿刺的細胞學檢查發現有組織漿菌的感染。血液培養長出 Aspergillus niger。在住院的第四天，病人發生敗血性休克；急性腎衰竭和呼吸衰竭。我們給與每天 50 毫克的 amphotericinB。但這病人仍於住院的第五天死亡。

Figure 1A　　Figure1B

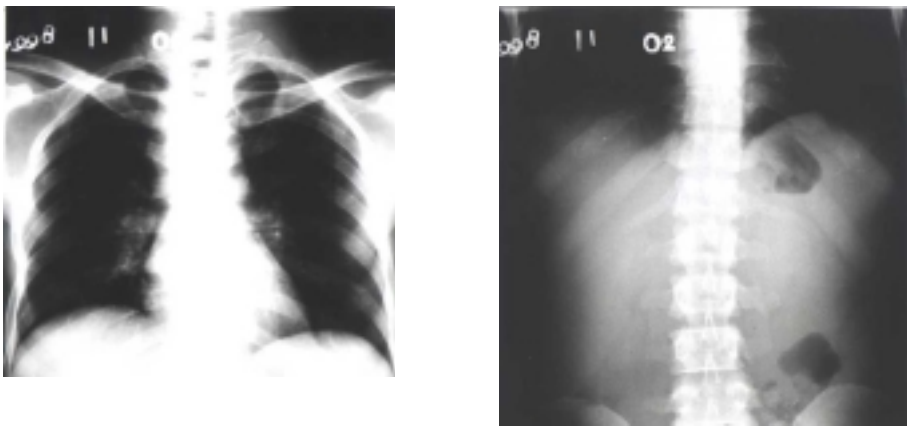

Figure 1. Chest roentgenogram(1A) and radiography of the abdomen(1B) showed negative finding.

Figure 2A

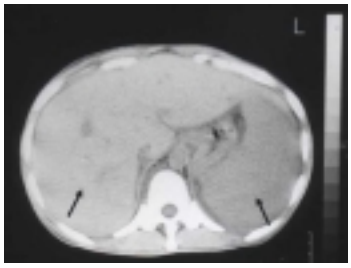

Figure2B

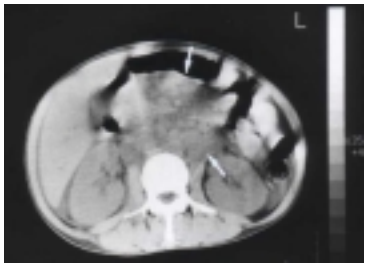

Figure2C

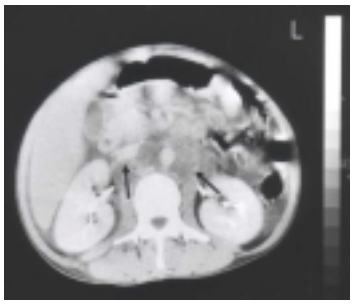

Figure2D

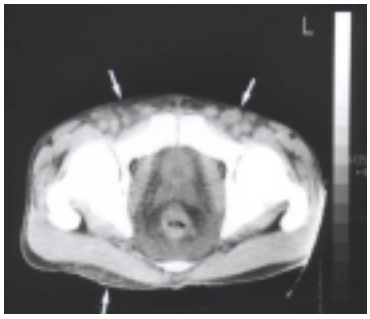

Figure 2. 2A: Hepatomegaly (right arrow) and splenomegaly(left arrow).
2B: Lymphadenopathy in the periaortic area (lower arrow) and infiltration in mesentary area (upper arrow).
2C: Enhanced CT showed periaortic lymphadenopathy (right arrow), and that inferior vena cava was shifted backward by enlarged lymph nodes (left arrow).
2D: Lymphadenopathy in bilateral inguinal area (upper arrow) and infiltration in the subcutaneous tissue (lower arrow).

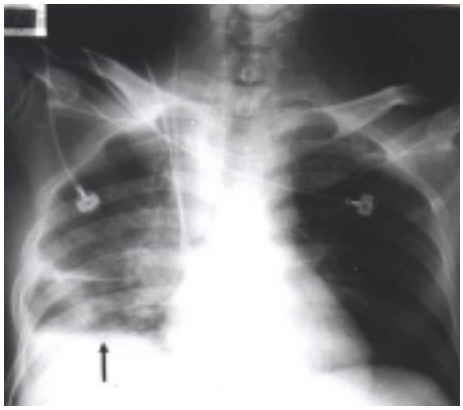

Figure 3. Chest roentgenogram showed right pleural effusion (arrow).

Figure 4A

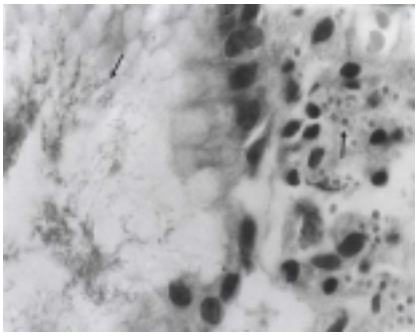

Figure4B

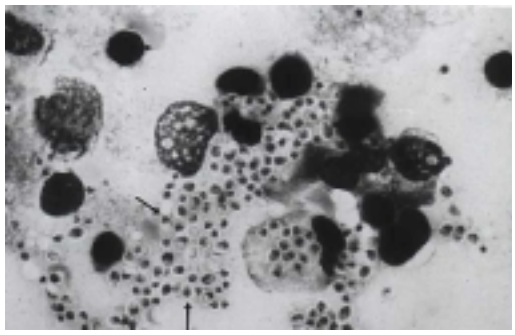

Figure 4. 4A: Stomach biopsy showed fungal infection (left arrow) and helicobacter pylori bacteria infection (right arrow) within ulcer.

4B: Periodic acid-Schiff(PAS) stain revealed positive staining of the fungus and discernable capsule formation of the yeast -like microorganism.