Pneumocystis carinii Pneumonia, Pulmonary Tuberculosis and Visceral Leishmaniasis in an Adult HIV Negative Patient

Antonio Carlos Toledo Jr. and Márcio Rodrigues de Castro

Eduardo Menezes Hospital, Hospitalar Foundation of Minas Gerais, MG, Brazil

This is a case report of a 29 year old male with pneumocystis pneumonia and tuberculosis, and who was initially suspected of having HIV infection, based on risk factor analyses, but was subsequently shown to be HIV negative. The patient arrived at the hospital with fever, cough, weight loss, loss of appetite, pallor, and arthralgia. In addition, he was jaundiced and had cervical lymphadenopathy and mild heptosplenomegaly. He had interstitial infiltrates of the lung, sputum smears positive for *Mycobacterium tuberculosis* and *Pneumocystis carinii*, and stool tests were positive for *Strongyloides stercoralis* and *Schistosoma mansoni*. He was diagnosed as having AIDS, and was treated for tuberculosis, pneumocystosis, and strongyloidiasis with a good response. The patient did not receive anti-retroviral therapy, pending outcome of the HIV tests. A month later, he was re-examined and found to have worsening hepatosplenomegaly, pancytopenia, fever, and continued weight loss. At this time, it was determined that his HIV ELISA antibody tests were negative. A bone marrow aspirate was done and revealed amastigotes of leishmania, and a bone marrow culture was positive for *Leishmania* species. He was treated with pentavalent antimony, 20 mg daily for 20 days, with complete remission of symptoms and weight gain. This case demonstrates that immunosuppression from leishmaniasis and tuberculosis may lead to pneumocystosis, and be misdiagnosed as HIV infection. The occurrence of opportunistic infections in severely ill patients without HIV must always be considered and alternate causes of immunosuppression sought.

Key Words: *Pneumocystis carinii*, visceral leishmaniasis, tuberculosis, HIV diagnosis, opportunistic infections.

We describe a case of *P. carinii* pneumonia as a complication of visceral leishmaniasis in an HIV negative patient. Visceral leishmaniasis (VL) is a chronic infectious disease characterized by an important immunological dysfunction that predisposes to other infections, mainly involving the pulmonary and gastrointestinal systems. In Brazil, bacterial pneumonia and tuberculosis are frequent opportunistic infections in this disease. *P. carinii* is a ubiquitous organism that commonly causes disease in immunodeficient patients such as in cancer, HIV/AIDS, leukemia, lymphoma, and transplant recipients [1]. Although there is no description of *P. carinii* pneumonia as an opportunistic infection of VL in the medical literature, it is plausible that immunodysfunction induced by Leishmania could be responsible for this patient's illness. If so, this would be the first description of an association of VL and *P. carinii* pneumonia.

Received on 31 March 2001; revised 27 May 2001.
Address for correspondence: Dr. Antonio Carlos Toledo Jr. Rua Mário Coutinho, 541/304, Zip code: 30570-310 – Belo Horizonte – MG – Brazil. Phone (55 31) 3290-2968. Fax (55 31) 3290-2977.

The Brazilian Journal of Infectious Diseases 2001;5(3):154-157

1413-8670

Case report

A 29 year old male patient, was admitted to Hospital Eduardo de Menezes (Infectious Diseases Hospital of Minas Gerais State, Brazil) on October 16, 1995. He complained of fever, asthenia, weight loss (>10 kg), loss of appetite, generalized arthralgia and a productive cough. Past history indicated 2 blood transfusions and

unsafe heterosexual sexual practice with multiple partners, including female prostitutes in Santos (the largest Brazilian port city, and a very high prevalence of HIV/AIDS). Physical exam showed jaundice, pallor, cervical lymphadenopathy, and mild hepatosplenomegaly. Laboratory tests showed anemia (hemoglobin 8.2 mg/dl), leukopenia (1,700 cells/ mm^3), and a normal platelet count (143,000). Chest radiography revealed mild interstitial infiltrates. Sputum smear identified *Mycobacterium tuberculosis* (3 samples) and *Pneumocystis carinii* (histology – 1 sample). A blood sample for HIV serology was taken after the proper consent was obtained. Other laboratory findings were: blood smear negative for malaria, stool exams showed *Strongyloides stercoralis* and *Schistosoma mansoni*, blood cultures negative (2 samples), sputum cultures negative (2 samples), VDRL negative, FTA-Abs positive, and HbsAg negative.

The initial diagnoses were: schistosomiasis mansoni, strongyloidiases, disseminated tuberculosis, *P. carinii* pneumonia, and possible HIV infection. There was a good response to specific treatment including oxamniquine; thiabendazole; rifampin, isoniazid and pyrazinamide; and co-trimoxazole in high dose (15 mg of trimethoprim/kg/day), respectively. He was discharged in a very good condition on November 9, 1995, and referred to the hospital outpatient clinic. The HIV serologic test results were not available at the time of discharge.

The patient did not go to the outpatient clinic and, on December 20, he was hospitalized again with the same symptoms (fever, moderate hepatosplenomegaly and significant weight loss). At that time, he also had a low platelet count associated with persistent anemia and leukopenia. Clinical deterioration was associated with reduction of co-trimoxazole dose from a therapeutic to a prophylactic one (2,400 mg to 800 mg of trimethoprim/day). He had continued regular use of the antituberculosis drugs. Serologic testing for HIV on two different samples was negative by ELISA for HIV antibodies. Stool and sputum exams were negative, showing good response to schistosomiasis, strongyloidiasis, and tuberculosis treatments.

Re-evaluation of the case was done. This was a male young adult patient with fever, moderate hepatosplenomegaly, pancytopenia, and cachexia (weight loss >15 kg) who was not infected with HIV. At this point, the differential diagnosis was changed to include: visceral leishmaniasis (VL), leukemia, lymphoma, and histoplasmosis. The epidemiological history identified possible cases of VL in his neighborhood. Bone marrow aspiration smear and culture identified *Leishmania* sp., confirming visceral leishmaniasis (kala-azar) as a main diagnosis. VL treatment was initiated on December 29, with meglumine antimonate (Glucatime®) at a dose of 20 mg of antimoniate/kg/day for 20 days. There was complete remission of symptoms. On January 18, 1996, the patient was discharged and referred to the outpatient clinic. At that time he had a weight gain of 15 kg, mild hepatosplenomegaly, and no other symptoms.

Discussion

The initial presentation was compatible with an advanced HIV infection phase complicated by disseminated tuberculosis and *P. carinii* pneumonia. Anemia, leukopenia, mild hepatosplenomegaly, and cachexia could be explained by HIV or by tuberculosis [2-9]. At that time, the patient did not present a low platelet count, a frequent observation in kala-azar [10]. Fever, cough, and a radiologic image of interstitial infiltrate could be related to HIV, tuberculosis and *P. carinii* pneumonia [7-9]. A delay of HIV serology, and temporary VL response to high doses of co-trimoxazole contributed to the misdiagnosis of HIV infection and delayed the final diagnosis of kala-azar. Despite the low incidence of VL in urban areas of large Brazilian cities, it does exist and should be included in the differential diagnosis of any patient presenting fever, weight loss and low blood cell count.

Visceral leishmaniasis (VL) is an endemic disease in Brazil. During 1998, 1,809 new cases were reported to the Brazilian Ministry of Health [11]. VL is much more frequent in rural areas but, since the 1980s, urban autochtonous cases are being reported in large cities such as São Paulo, Rio de Janeiro, Belo Horizonte,

Salvador, Natal, and Teresina [12-19]. Urban outbreaks are related to domestic dog infection [20, 21].

VL is characterized by an important immunological dysfunction. Ill patients do not develop a protective Th1 cell-mediated immune response, and delayed hypersensitivity responses are absent. An *in vitro* study showed that mononuclear cells do no proliferate and fail to produce interferon-γ and interleukin-2 in response to leishmanial antigens. Despite these, antileishmanial antibodies are produced at high titers by patients with progressive disease, and a hypergammaglobulinemia (polyclonal T-cell activation) is often observed [10, 22-24].

Leishmania has a great affinity to the reticuloendothelial system (RES). After inoculation, promastigotes forms convert to amastigotes in macrophages and disseminate through the RES, to mononuclear phagocytes. RES hyperplasia and hypertrophy are observed with disease progression. Reticuloendothelial modifications are easily observed in liver, spleen, and bone marrow. Besides RES involvement, inflammatory response against the parasite in interstitial tissues is the pathological base pf other organ manifestations (chest, bowel, skin, kidney) [10, 24, 25].

VL clinical manifestations vary according the degree of immunodeficiency. The incubation period ranges from 3 to 8 months, but can be as long as 34 months [14]. Commonly, patients present an insidious disease with gradual onset of symptoms. Fever, weakness, loss of appetite, splenomegaly, hepatomegaly, and weight loss are more frequently observed. Involvement of lung, pleura, oral mucosa, and small intestine are less frequent. Laboratory findings include anemia, leukopenia, low platelet count, and hypergammaglobulinemia [24-27].

Differential diagnosis includes malaria, schistosomiasis, typhoid fever, disseminated tuberculosis, histoplasmosis, prolonged Salmonella bacteremia, leukemia, lymphoma, and Gaucher's disease, among others [10, 24, 25, 30, 31].

A prevalent antimonial is the first choice for the initial treatment of VL. Recommended dose is 20 mg of antimoniate/kg/day intravenous or intramuscular for 20 to 30 days. Patients should be hospitalized in the beginning of treatment because of possible serious adverse reactions. Interferon-γ combined with pentavalent antimonial showed good response in patients who failed the antimonial alone, or relapsed after treatment [10, 24, 25]. There are some reports of temporary response to co-trimoxazole in high doses in refractory cases [32-35].

This case report emphasizes the need to search for all possible causes of immunosuppression in patients with opportunistic infections, not to assume that HIV infection is the causative immunosuppressive agent.

References

1. Walzer P. Pneumocystis pneumonia. In: Mandell G., Bennett J., Dolin R., eds. Principles and Practice of Infectious Diseases. Vol. 2. New York: Churchill Livingstone **1995**:2478-5487.
2. Picon P., Rizzon C., Hoefel Filho J. Tuberculose de Disseminação Hemática. In: Picon P., Rizzon C., Ott W., eds. Tuberculose. Epidemiologia, Diagnóstico e Tratamento em Clínica e Saúde Pública. Rio de Janeiro: Medsi, **1993**.
3. Doweiko J., Groopman J. Hematologic Complications of human immunodeficiency virus infection. In: De Vita Jr. V., Hellman S., Rosenberg S., eds. AIDS: Biology, Diagnosis, Treatment and Prevention. Philadelphia: Lippincott-Raven, **1997**.
4. Goldenberg A. Hematologic abnormalities and mycobacterial Infections. In: Rom W., Garay S., eds. Tuberculosis. Boston: Little, Brown, **1996**.
5. Hambleton J. Hematologic Complications of HIV infection. In: Sande M., Volberding P., eds. The Medical Management of AIDS. Philadelphia: WB Saunders, **1997**.
6. Oyer R., Schlossberg D. Hematologic changes in tuberculosis. In: Schlossberg D., ed. Tuberculosis. New York: Springer-Verlag, **1994**.
7. Afiune J. Tuberculose. Clínica e Diagnóstico. In: Veronesi R., Foccacia R., eds. Veronesi Tratado de Infectologia. São Paulo: Atheneu, **1996**.
8. Hollander H. Initiating routine care for the HIV-infected adult. In: Sande M., Volberding P., eds. The Medical Management of AIDS. Philadelphia: WB Saunders, **1997**.
9. Saag M. Clinical spectrum of human immunodeficiency virus disease. In: De Vita Jr. V., Hellman S., Rosenberg S., eds. AIDS: Biology, Diagnosis, Treatment and Prevention. Philadelphia: Lippincott-Raven, **1997**.

10. Badaró R., Duarte M. Leishmaniose visceral (Calazar). In: Veronesi R, Foccacia R, eds. Veronesi Tratado de Infectologia. Vol. 2. São Paulo: Atheneu, **1996**:1234-59.
11. Ministério da Saúde. Casos notificados de doenças por UF e período especificado e acumulado no ano, Brasil, 1997 e 1998. Boletim Epidemiológico **1998**;III:3.
12. Amato Neto V., Blanco Filho F. Leishmaniose visceral adquirida no estado de São Paulo (Brasil). Rev Saude Publica **1981**;15:643-5.
13. Iversson L., Pires R., Ribeiro M., et al. Investigação epidemiológica de um novo caso de leishmaniose visceral ocorrido na grande São Paulo, Brasil. Revista de Saúde Pública **1982**;16:205-19.
14. Marzochi M., Coutinho S., de Souza W., et al. Canine visceral leishmaniasis in Rio de Janeiro, Brazil. Clinical, parasitological, therapeutical and epidemiological findings (1977-1983). Memórias do Instituto Oswaldo Cruz **1985**;80:349-57.
15. Genaro O., da Costa C., Williams P., et al. Ocorrência de calazar em área urbana da grande Belo Horizonte, MG. Revista da Sociedade Brasileira de Medicina Tropical **1990**;23:121.
16. Costa C., Pereira H., Araujo M. Visceral leishmaniasis epidemic in the State of Piaui, Brazil, 1980-1986. Rev Saud Publica **1990**;24:361-72.
17. Jeronimo S., Oliveira R., Mackay S., et al. An urban outbreak of visceral leihmaniasis in Natal, Brazil. Trans Royal Soc Trop Med Hyg **1994**;88:386-8.
18. Cunha S., Freire M., Eulalio C., et al. Visceral leishmaniasis in a new ecological niche near a major metropolitan area of Brazil. Trans Royal Soc Trop Med Hyg **1995**;89:155-8.
19. Luz K., da Silva V., Gomes E., et al. Prevalence of anti-*Leishmania donovani* antibody among Brazilian blood donnors and multiply transfused hemodialysis patients. Amer J Trop Med **1997**;57:168-71.
20. Guardia J. Co-trimaxazole for kala-azar. Lancet **1981**;1:501-2.
21. Arias J., Monteiro P., Zicker F. The re-emergence of visceral leishmaniasis in Brazil. Emerging Infectious Diseases **1996**;2:145-6.
22. Campos-Neto A., Bunn-Moreno M. Polyclonal B cell activation in hamsters infected with parasites of the genus *Leishmania*. Infect Immun **1982**;38:871-6.
23. Carvalho E.M., Bacellar O., Barral A., et al. Antigen-specific immunosuppression in visceral leishmaniasis is cell mediated. J Clin Invest **1989**;83:860-4.
24. Pearson R., Sousa A. Leishmania species: visceral (kala-azar), cutaneous, and mucosal leishmaniasis. In: Mandell G., Bennett J., Dolin R., eds. Principles and Practice of Infectious Diseases. Vol. 2. New York: Churchill Livingstone, **1995**:2428-42.
25. Mardsen P., Johnson Jr. W. Leishmania. In: Gorbach S, Bartlett J, Blacklow N, eds. Infectious Disease. Philadelphia: WB Saunders, **1998**:2420-6.
26. Badaro R., Jones T.C., Carvalho E.M., et al. New perspectives on a subclinical form of visceral leishmaniasis. J Infect Dis **1986**; 154:1003-11.
27. Badaro R., Jones T.C., Lorenco R., et al. A prospective study of visceral leishmaniasis in an endemic area of Brazil. J Infect Dis **1986**;154:639-49.
28. Berenguer J., Moreno S., Cercenado E., et al. Visceral leishmaniasis in patients infected with human immunodeficiency virus (HIV). Ann Intern Med **1989**;111:129-32.
29. Montalban C., Calleja J.L., Erice A., et al. Visceral leishmaniasis in patients infected with human immunodeficiency virus. Co-operative Group for the Study of Leishmaniasis in AIDS. J Infect **1990**;21:261-70.
30. Medrano F.J., Hernandez-Quero J., Jimenez E., et al. Visceral leishmaniasis in HIV-1-infected individuals: a common opportunistic infection in Spain? AIDS **1992**;6:1499-503.
31. Peters B.S., Fish D., Golden R., et al. Visceral leishmaniasis in HIV infection and AIDS: clinical features and response to therapy. Q J Med **1990**;77:1101-11.
32. Thakur C., Sinha P. Inefficacy of ethambutol, ethambutol plus isoniazid, INH plus rifampicin, co-trimoxazole and metronidazole in the treatment of kala-azar. Journal of Tropical Medicine and Hygiene **1989**;92:383-5.
33. Rodrigues-Cuartero A., Perez-Blanco F., Lopez-Fernandez A. Co-trimoxazole for visceral leishmaniasis. Infection **1990**;18:40.
34. Murphy K., Bong A. Co-trimoxazole for systemic leishmaniasis. Lancet **1981**;1:323-4.
35. Chatterjee S., Chatterjee R. Visceral leishmaniasis treated with rifampicin and co-trimoxazole. Journal of the Indian Medical Association **1994**;92:307.