Postepy Hig Med Dosw. (online), 2008; 62: 1-3
e-ISSN 1732-2693

www.phmd.pl
Case Report

Received: 2007.09.28
Accepted: 2007.12.14
Published: 2008.01.14

Cutaneous cryptococcosis as a rare manifestation of the immune reconstitution syndrome in an HIV-1-infected patient

Skórna postać kryptokokozy jako rzadko występujący objaw zespołu rekonstrukcji immunologicznej u pacjenta zakażonego HIV-1

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Immune reconstitution syndromes (IRS) in HIV-1-infected patients are associated with an exaggerated inflammatory response against an opportunistic infection during highly active antiretroviral therapy (HAART). The most commonly described cases of this phenomenon concern mycobacterial (*Mycobacterium avium* and *M. tuberculosis*) infections, pneumocystodosis, cryptoccoccal meningitis, and CMV infections. Cutaneous cryptococcosis as IRS is less commonly observed. The case of a 45-year-old HIV-1-positive male is reported who developed subcutaneous abscesses due to *Cryptococcus neoformans* infection after four weeks of effective HAART following profound immune deficiency.

Key words: **immune reconstitution disease • immune reconstitution syndrome • HIV-1 infection • cryptococcosis**

Streszczenie

Zespoły rekonstrukcji immunologicznej (ZRI) u pacjentów zakażonych HIV-1 są związane z rozwojem nadmiernej reakcji zapalnej w odpowiedzi na zakażenia oportunistyczne. Rozwijają się podczas stosowania skutecznej, wysoce aktywnej kombinowanej terapii antyretrowirusowej (highly active antiretroviral therapy – HAART). Najczęściej obserwuje się wystąpienie ZRI w przebiegu zakażenia prątkami (*Mycobacterium avium* i *M. tuberculosis*), pneumocystodozy, kryptokokowego zapalenia opon mózgowo-rdzeniowych, zakażenia CMV. Rzadziej stwierdza się jako ZRI skórną postać kryptokokozy. Poniżej przedstawiamy przypadek 45-letniego mężczyzny, u którego obserwowano ropnie podskórne wskutek zakażenia *Cryptococcus neoformans*. U pacjenta stwierdzano zaawansowany niedobór odporności. Zmiany na skórze pojawiły się w cztery tygodnie po włączeniu skutecznej terapii antyretrowirusowej.

Key words: **choroba rekonstrukcji immunologicznej • zespół rekonstrukcji immunologicznej • zakażenie HIV-1 • kryptokokoza**

Full-text PDF: http://www.phmd.pl/pub/phmd/vol_62/11529.pdf

Word count: 763
Tables: –
Figures: 1
References: 18

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Background

Highly active antiretroviral therapy (HAART) usually leads to an improvement in the immune response. This immune recovery is due to the suppression of viral replication and is accompanied by improvement in the clinical picture. [1]. However, despite a CD4 T-cell rise, atypical symptoms of opportunistic infections may occur in some patients [4,12,13,15]. These diseases are associated with a paradoxical immune inflammatory reaction to subclinical or preexistent infection and are referred to as IRIS (immune restoration inflammatory syndrome), IRS (immune reconstitution syndrome/immune recovery syndrome), or IRD (immune restoration disease) [4,15]. The most commonly described cases of this phenomenon concern mycobacteriosis (*Mycobacterium avium* and *M. tuberculosis* infections), pneumocystodosis, cryptoccoccal meningitis, and CMV infections, [5,10,12,13,14]. Cutaneous cryptococcosis as an IRS is less commonly observed [6,9,13]. Here we report the case of a 45-year-old HIV-1-positive male who developed subcutaneous abscesses due to *Cryptococcus neoformans* infection after four weeks of effective HAART following profound immune deficiency.

Case report

A 45-year-old man was probably infected in 1985 through heterosexual contact. HIV-1 infection was diagnosed in 1995 and the CD4 T-cell count was 77 cells/µl. HAART (zidovudine + didanozine + saquinavir-hgc, changed to indinavir in 1998) was initiated for the first time in 1997, but the therapy was not successful and a continuous decline in CD4 T-cell count (to 4 cells/µl) and a high viral load (>14 log copies/ml) were seen. For this reason the regimen was changed in February 1999. The patient received stavudine, lamivudine, nelfinavir, and efavirenz. After four weeks of such treatment, multiple subcutaneous abscesses involving the skin of the head, face, ears, neck, and upper part of the chest suddenly developed within a few days. These skin lesions resembled *molluscum contagiosum* and were accompanied by high-grade fever and symptoms of bilateral pneumonia, which resolved spontaneously within two weeks. No neurological abnormalities were examined found and no lymph nodes were enlarged. During the next few days the patient's status worsened, with ulceration of the skin lesions (Figure 1). Histopathological examination and mycological cultures of a skin biopsy as well as blood cultures revealed *C. neoformans*. Cryptococcal antigen was also identified in the blood. The patient started treatment with amphotericin B intravenously. He received increasing doses of the drug, up to 50 mg/day, and HAART was continued. This therapy led to a very rapid improvement. After four days of the treatment, gradual regression of the skin ulcers was observed and on the fifth day the patient stopped having high-grade fever. After two weeks of treatment, both blood cultures and serum antigen assay were negative for *C. neoformans*. In spite of this, amphotericin B was continued for one more week (a total of three weeks), then fluconazole (100 mg once per day orally) was used for three months.

Figure 1. Cryptococcal ulcerations of the skin due to the immune reconstitution syndrome in a HIV-1-positive man

The CD4 T-cell count and HIV RNA were measured two weeks after resolution of the symptoms. A significant increase in the CD4 T-cell count compared with the results at the time of initiation of the second ARV regimen (31 vs. 4 cells/µl) and a rapid decline in viral load (6.3 vs. 4.07 log copies/ml) were revealed. Within the next eight weeks a further rise in the CD4 T-cell count was observed (up to 119 cells/µl) and HIV RNA reached undetectable levels by ultrasensitive PCR (Roche). No more symptoms of any IRS have been observed.

Discussion

Cutaneous cryptococcosis was accompanied by a rapid improvement in a profoundly deteriorated immune response which followed effective HAART. No signs and symptoms of any opportunistic infection (OI) had been previously established in the patient. This was an unexpected event that occurred after the initiation of potent HAART. There was a temporal association between the institution of favorable antiretroviral therapy and the development of IRS. The atypical presentation of cryptoccosis was due to altered restoration of the immune responses to

an opportunistic pathogen followed by tissue inflammation. Our observations are consistent with other reports [6,9,13] indicating that this manifestation of IRS is uncommon and concerns cases with a very low CD4 T-cell count followed by a rapid improvement. The incidence of cryptococcal subcutaneous abscesses is limited compared with other IR-cryptococcosis manifestations [2,3,7,8, 11,14,16,17,18]. As it does not happen very often, it is an unexpected manifestation with atypical signs and symptoms resembling other diseases. That is why one cannot suspect it at once.

Conclusions

1. In any case of advanced immune deficiency followed by effective HAART, immune reconstitution inflammatory syndrome should be expected.
2. Manifestation of subcutaneous abscesses after commencing effective HAART may be due to IRS-cryptococcosis.
3. Antifungal treatment with amphotericin B is effective in IR-cutaneous cryptococcosis. There is no necessity to interrupt cART when no other organs are involved.

References

[1] Bartlett J.A., DeMasi R., Quinn J., Moxham C., Rousseau F.: Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. AIDS, 2001; 15: 1369–1377

[2] Blanche P., Gombert B., Ginsburg C., Passeron A., Stubei I., Rigolet A., Salmon D., Sicard D.: HIV combination therapy: immune restitution causing cryptococcal lymphadenitis dramatically improved by anti-inflammatory therapy. Scand. J. Infect. Dis., 1998; 30: 615–616

[3] Breton G., Seilhean D., Cherin P., Herson S., Benveniste O.: Paradoxical intracranial cryptococcoma in a human immunodeficiency virus-infected man being treated with combination antiretroviral therapy. Am. J. Med., 2002; 113: 155–157

[4] French M.A., Price P., Stone S.F.: Immune restoration disease after antiretroviral therapy. AIDS, 2004; 18: 1615–1627

[5] Furrer H., Malinverni R.: Systemic inflammatory reaction after starting highly active antiretroviral therapy in AIDS patients treated for extrapulmonary tuberculosis. Am. J. Med., 1999; 106: 371–372

[6] Ingram P.R., Howman R., Leahy M.F., Dyer J.R.: Cryptococcal immune reconstitution inflammatory syndrome following alemtuzumab therapy. Clin. Infect. Dis., 2007; 44: e115–e117

[7] Jenny-Avital E.R., Abadi M.: Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. Clin. Infect. Dis., 2002; 35: e128–e133

[8] Lanzafame M., Trevenzoli M., Carretta G., Lazzarini L., Vento S., Concia E.: Mediastinal lymphadenitis due to cryptococcal infection in HIV-positive patients on highly active antiretroviral therapy. Chest, 1999; 116: 848–849

[9] Manfredi R., Pieri F., Pileri S.A., Chiodo F.: The changing face of AIDS-related opportunism: cryptococcosis in the highly active antiretroviral therapy (HAART) era. Case reports and literature review. Mycopathologia, 1999; 148: 73–78

[10] Salama C., Policar M., Venkataraman M.: Isolated pulmonary *Mycobacterium avium* complex infection in patients with human immunodeficiency virus infection: case reports and literature review. Clin. Infect. Dis., 2003; 37: e35–e40

[11] Shelburne S.A. III, Darcourt J., White A.C. Jr., Greenberg S.B., Hamill R.J., Atmar R.L., Visnegarwala F.: The role of immune reconstitution inflammatory syndrome in AIDS-related *Cryptococcus neoformans* disease in the era of highly active antiretroviral therapy. Clin. Infect. Dis., 2005; 40: 1049–1052

[12] Shelburne S.A. III, Hamill R.J.: The immune reconstitution inflammatory syndrome. AIDS Rev., 2003; 5: 67–79

[13] Shelburne S.A. III, Hamill R.J., Rodriguez-Barradas M.C., Greenberg S.B., Atmar R.L., Musher D.W., Gathe J.C. Jr., Visnegarwala F., Trautner B.W.: Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. Medicine (Baltimore), 2002; 81: 213–227

[14] Shelburne S.A. III, Visnegarwala F., Darcourt J., Graviss E.A., Giordano T.P., White A.C. Jr., Hamill R.J.: Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. AIDS, 2005; 19: 399–406

[15] Stoll M., Schmidt R.E.: Immune restoration inflammatory syndromes: the dark side of successful antiretroviral treatment. Curr. Infect. Dis. Rep., 2003; 5: 266–276

[16] Trevenzoli M., Cattelan A.M., Rea F., Sasset L., Semisa M., Lanzafame M., Meneghetti F., Cadrobbi P.: Mediastinitis due to cryptococcal infection: a new clinical entity in the HAART era. J. Infect., 2002; 45: 173–179

[17] Trevenzoli M., Lanzafame M., Lazzarini L., Carretta G., Vento S., Concia E.: *Esophageal cryptococcosis* in a patient with AIDS. Am. J. Gastroenterol., 1999; 94: 1981–1982

[18] Woods M.L. II, MacGinley R., Eisen D.P., Allworth A.M.: HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. AIDS, 1998; 12: 1491–1494