Paradoxical Worsening in Tuberculosis during Therapy in an HIV-Infected Patient

Introduction

Paradoxical worsening of tuberculosis during therapy is still an intriguing matter for all clinicians, because it is difficult to decide if there is perhaps an underlying disease or if tuberculous bacilli are resistant to chemotherapy. We report here the case of an HIV-infected patient who developed unilateral pleural effusion 7 weeks after initiation of antituberculous treatment for miliary tuberculosis.

Case Report

A 35-year-old man was hospitalized because of fever, chest pain and weight loss. His medical history was unremarkable and he had never taken any medication. On physical examination diffuse rhonchi and splenomegaly were found. There were no focal neurological signs. His temperature was 39.8° C. Laboratory findings were: WBC count, 2,800/mm^3; platelet count, 108,000/mm^3; hemoglobin, 10.7 g/dl; GOT, 120 IU/l; GPT, 90 IU/l, gamma-GT, 324 IU/l; alkaline phosphatase, 310 IU/l; bilirubin, 10 µMol/l.

Radiographic studies showed diffuse micronodular opacities. BAL, sputum and liver biopsy examination were positive for *Mycobacterium tuberculosis*. CSF examination was normal. No other microorganism was found in any of these samples. Serological studies for HIV and hepatitis B virus were positive. The CD4$^+$ cell-count was 56/mm^3. Intravenous treatment with isoniazid, rifampin and ethambutol was begun. The patient improved within a few days. Oral treatment was substituted for intravenous therapy after 2 weeks.

Seven weeks after introduction of antituberculous therapy the patient complained for the first time about shortness of breath, cough and chest pain. He was afebrile and had a respiratory rate of 28/min, a heart rate of 100/min, and blood pressure of 100/60 mmHg. Blood gas analysis while breathing room air showed: pH, 7.47; PaO_2, 56 mmHg, and $PaCO_2$, 27 mmHg. Chest X-ray showed pleurisy with extensive unilateral effusion. Drainage produced about 1,000 ml per day of a brownish fluid for 3 days. Chemical analysis of the fluid showed the following values: glucose, 5 mMol/l; protein, 54 g/l. Microscopic examination, bacterial and fungal cultures, AFB-smears, mycobacterial culture and pleural biopsy were negative. *M. tuberculosis* organisms cultured from the first BAL and sputum smears were susceptible to isoniazid, rifampin and ethambutol. Pleurisy was therefore attributed to an inflammatory reaction to antituberculous therapy. Oral prednisolone (0.5 mg/kg/day), which was tapered gradually for the next week, was added to the regimen. The patient gradually improved and pleural effusion resolved after 10 days. He was discharged 2 weeks later and continued to take isoniazid, ethambutol and rifampin. Antiretroviral therapy with zidovudine and prophylactic treatment with trimethoprim-sulfamethoxazole were begun. Laboratory findings at discharge were: WBC count, 4,000/mm^3; hemoglobin, 11.8 g/dl, and platelet count, 165,000/mm^3. CD4$^+$ cell-count was 103/mm^3. Liver function tests, gamma-GT and alkaline phosphatase levels were normal. Chest X-ray examination showed no major sequelae.

Discussion

Our patient was admitted with a diagnosis of miliary tuberculosis. Laboratory evaluation revealed abnormal liver function and pancytopenia. A test for HIV-antibodies turned out to be positive and his CD4$^+$ cell count was only 56/mm^3. However, up to admission he was not known to be HIV-positive and he never had an HIV-related infection.

Peripheral blood changes are frequently associated with disseminated tuberculosis but pancytopenia remains rare [1]. Its incidence may be less than 6% [1, 2]. Yet, its pathogenesis is still not clearly established. Especially in cases where pancytopenia does not resolve completely under antituberculous therapy, an underlying primary haematologic disorder or another aetiology must be discussed. Hematological abnormalities are common and multiple in patients with acquired immune deficiency Syndrome (AIDS) and the occurrence of pancytopenia is frequent [3]. The causes of these changes are various and often associated, including the insult by the human immunodeficiency virus itself, drug reaction, infiltrative disease of the bone marrow and opportunistic infections [4]. Because of the rapid resolution of pancytopenia under antituberculous treatment alone, there is good reason to believe that pancytopenia was related to miliary tuberculosis. In addition, several reports have focused on this association which is a factor of poor outcome and is fatal in almost all cases [5, 6].

Seven weeks after initiation of treatment, the patient worsened and developed pleurisy. Prednisolone, which has been found to provide more rapid relief of clinical symptoms and absorption of pleural effusion [7], was added to the regimen.

Worsening of tuberculosis during therapy is intriguing, especially if culture and susceptibility results are not known. Paradoxical enlargement or development of intracranial tuberculomas during therapy is a well known phenomenon [8].

Some of the patients treated for tuberculous meningitis do worsen clinically for days or even weeks after introduction of antituberculous therapy, even if CT scan of the head with contrast material does not reveal tuberculoma or hydrocephalus. Yet, it is not clear if there were any microscopic tuberculomas. The addition of corticosteroids always improved patients' neurological status [9].

Recently, *Hill* et al. [10] reported three cases of tuberculous lymphadenitis in AIDS-patients, which exacerbated after up to 11 weeks after introduction of antituberculous treatment. This transient worsening in tuberculosis of the lymph nodes is well known and has already been described in immunocompetent patients before.

An HIV-infected patient with pancytopenia associated to disseminated tuberculosis continued to be increasingly ill despite antituberculous chemotherapy. Addition of prednisolone to his treatment achieved a dramatic improvement leading to cure [11].

Received: 11 January 1996/ Revision accepted: 22 April 1996

A. Mofredj, M. D., *J.-M. Guérin*, M. D., *F. Leibinger*, M. D., *R. Masmoudi*, M. D., Centre de Réanimation Médicale, Hôpital Lariboisière, 2, rue Ambroise Paré, F-75010 Paris, France.

The development of Adult Respiratory Distress Syndrome (ARDS) in miliary tuberculosis is extremly rare [1, 12], but its appearance after initiation of appropriate antibiotics is intriguing [12, 13]. *Onwubalili* et al. [13] reported two such cases. In addition, in their review of the literature they found several cases of patients who died unexpectedly and without obvious cause during treatment of tuberculosis. None of these patients had received corticosteroids, and clinical worsening developed early after initiation of antituberculous therapy.

To our knowledge, our case is the first one to report secondary development of extensive pleural effusion after initiation of treatment for disseminated tuberculosis.

Though the explanation for worsening during treatment remains unclear, in most cases this phenomenon occurs when tuberculosis is disseminated [5, 8, 13]. Dissemination leads to massive release of mycobacterial products inducing a production of high levels of inflammatory mediators after monocyte activation. Lipoarabinomannan from *M. tuberculosis* has been shown to induce the production of tumor necrosis factor from human macrophages [14], and it was speculated that lipoarabinomannan or other mycobacterial products may act *in vivo* like the lipopolysaccharide from gram-negative bacilli [15]. Introduction of lytic antibacterial therapy may sometimes initiate this process [12, 13]. Inflammatory mediators as well as mycobacterial components probably have a central role in pathogenesis of ARDS, pancytopenia [16] and in the paradoxical worsening of tuberculosis during therapy including secondary pleural effusion. Clinicians should be aware that initial worsening or development of new tuberculous lesions after introduction of specific treatment usually does not reflect treatment failure and that associated corticosteroid therapy may improve the outcome.

A. Mofredj, J.-M. Guérin, F. Leibinger, R. Masmoudi

References

1. **Maartens, G., Willcox, P. A., Benatar, S. R.:** Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. Am. J. Med. 89 (1990) 291–296.
2. **Cucin, R.. L., Coleman, M., Eckardt, J. J., Silver, R. T.:** The diagnosis of miliary tuberculosis: utility of peripheral blood abnormalities, bone marrow and liver needle biopsy. J. Chron. Dis. 26 (1973) 355–361.
3. **Hill, A. R., Premkumar, S., Brustein, S., Vaidya, K., Powell, S., Ping-Wu Li, Suster, B.:** Disseminated tuberculosis in the acquired immunodeficiency syndrome era. Am. Rev. Respir Dis. 144 (1991) 1164–1170.
4. **Scadden, D. T., Li, Z., Groopman, J. E.:** Pathophysiology and management of HIV associated hematologic disorders. Blood 74 (1989) 1455–1463.
5. **Rosenberg, M. J., Rumans, L. W.:** Survival of a patient with pancytopenia and disseminated coagulation associated with miliary tuberculosis. Chest 73 (1978) 536–539.
6. **Shrivastava, M. P., Madhu, S. V., Grover, A. K.:** Pancytopenia – a rare presentation of miliary tuberculosis. J. A. P. I. 41 (1993) 311.
7. **Lee, C.-H., Wang, W.-J., Lan, R.-S., Tsai, Y.-H., Chiang, Y.-C.:** Corticosteroids in the treatment of tuberculous pleurisy: a double-blind, placebo-controlled, randomized study. Chest 94 (1988) 1256–1259.
8. **Afghani, B., Liebermann, J. M.:** Paradoxical enlargement or development of intracranial tuberculomas during therapy: case report and review. Clin. Infect. Dis. 19 (1994) 1092–1099.
9. **Berenguer, J., Moreno, S., Laguna, F., Vicente, T., Adrados, M., Ortega, A., Gonzalez-La Hoz, A., Bouza, E.:** Tuberculous meningitis in patients infected with the Human Immunodeficiency Virus. N. Engl. J. Med 326 (1992) 668–672.
10. **Hill, A. R., Mateo, F., Hudak, A.:** Transient exacerbation of tuberculous lymphadenitis during chemotherapy in patients with AIDS. Clin. Infect. Dis. 19 (1994) 774–776.
11. **Masud, T., Kemp, E.:** Corticosteroids in treatment of disseminated tuberculosis in patient with HIV infection. Br. Med. J. 296 (1988) 464–465.
12. **Skurnik, Y., Zhornicky, T., Schattner, A.:** Survival in miliary tuberculosis complicated by respiratory distress. Presse Méd. 23 (1994) 979–981.
13. **Onwubalili, J. K., Scott, G. M., Smith, H.:** Acute respiratory distress related to chemotherapy of advanced pulmonary tuberculosis: a study of two cases and review of the literature. Q. J. Med. 59 (1986) 599–610.
14. **Moreno, C., Taverne, J., Mehlert, A., Bate, C. A. W., Brealy, R. J., Meager, A., Rook, G. A. W., Playfair, J. H. L.:** Lipoarabinomannan from *Mycobacterium tuberculosis* induces the production of tumor necrosis factor from human and murine macrophages. Clin. Exp. Immunol. 76 (1989) 240–245.
15. **Ahuja, S. S., Ahuja, S. K., Phelps, K. R., Thelmo, W., Hill, A. R.:** Hemodynamic confirmation of septic shock in disseminated tuberculosis. Crit. Care Med. 20 (1992) 901–903.
16. **Benatar, S. R., McLoud, T. C., Mark, E. J.:** Case 23-1995. Case records of the Massachusetts General Hospital. N. Engl. J. Med. 333 (1995) 241–248.

Book Review

H. Koprowski, H. Meada (eds.)
The Role of Nitric Oxide in Physiology and Pathophysiology
90 pages, 21 figures
Springer, Berlin–Heidelberg–New York–London–Paris–Tokyo–Hong Kong, 1995
Price: DM 139,– DM

This book contains eight contributions presented at a workshop in Philadelphia in 1993. Each contribution of this thin 90-page book is written by specialists in this area and gives a comprehensive overview of the special physiological and pathophysiological aspects of nitric oxide, e.g. "S-Nitrosothiols and the Bioregulatory Actions of Nitrogen Oxides through Reactions with Thiol Groups;" "A New Nitric Oxide Savenger, Imidazolineoxyl N-Oxide Derivative, and Its Effects in Pathophysiology and Microbiology;" "The Role of Nitric Oxide in the Pathogenesis of Virus-Induced Encephalopathies." The reference list at the end of the concise contributions provides a quick orientation in field and many of the separate papers have excellent figures. On the whole, the book could be of interest to insiders in research on nitric oxide, since renown scientists present exceptional but detailed information on this subject. However, it seems less suitable for the reader who, from the title, expects a quick survey of the physiological and pathophysiological significance of NO.

H.-W. Pfister
München