Brief Reports

Acute HIV Seroconversion Presenting with Active Tuberculosis and Associated with High Levels of T-Regulatory Cells

Omar Sued,[1] María Florencia Quiroga,[2] María Eugenia Socías,[1]
Gabriela Turk,[2] Horacio Salomón,[2] and Pedro Cahn[1]

Abstract

A patient with well-defined acute HIV infection who developed concomitant pulmonary tuberculosis during the retroviral acute syndrome is reported here. In this patient high levels of T-regulatory cells (Tregs) and a low proliferation response to *M. tuberculosis* were initially detected, which normalized throughout follow-up. This case calls for the consideration of tuberculosis in patients in the early stages of HIV, and emphasizes the need for further study of the potential causal relationship between Treg cells and the risk of TB reactivation in HIV patients.

Introduction

ACUTE HIV INFECTION IS CHARACTERIZED BY A HIGHLY IMMUNE-ACTIVATED STATE and a massive depletion of CD4 cells due to multiple mechanisms (1). Most patients present with a febrile illness 2–3 weeks from HIV exposure, which usually resolves spontaneously, although some cases present with severe disease with neurological or systemic involvement (2), and/or development of opportunistic diseases. Esophageal candidiasis, toxoplasmic encephalitis, *Pneumocystis jirovecii* pneumonia, or cytomegaloviral disease have been reported and were attributed to CD4 depletion during acute HIV infection. However, as far as we know there are no reported cases of active *Mycobacterium tuberculosis* disease concomitantly with acute HIV infection. The only report of mycobacterial infection involved the presentation of *M. kansasii* in an HIV seroconverter (3).

Regulatory T cells (Tregs) have been implicated in the modulation of immune responses to avoid overactive immunity. In HIV infection, following the initial acute infection, Tregs are upregulated and may contribute to suppression of anti-HIV immunity, promoting acute viremia and facilitating persistent infection, while in chronic infection gradual depletion of these cells allows the development of immune activation (4,5). On the other hand, patients with tuberculosis (TB) present with an upregulation of Tregs, which contributes to decreased production of interferon-γ and IL-10 and suppresses immune responses to TB antigens (6,7). In addition, individuals latently infected by TB present with a rapid depletion of *M. tuberculosis*-specific Th-1 cells during the acute phase of HIV infection due to direct viral infection of these cells, mostly expressing the surface co-receptor CCR5 (8).

Case Report

In May of 2008 a 33-year-old man was examined because of high fever and night sweats of 5 days' duration, skin rash, and oral and perianal ulcers. He denied having cough or expectoration, or close contact with anyone with cough or confirmed TB. His medical history included frequent use of inhaled cocaine, risky sexual behavior with multiple unprotected sexual relationships with women and men in the past months, syphilis treated 4 y prior, and a positive hepatitis C serology in 2004. Abnormal laboratory values included WBC count 3400 cells/μL, hemoglobin 15.6 g/L, platelets 90,000/μL, AST 74 U/L, and ALT 108 U/L. A chest x-ray and serologic studies (including HIV) were ordered, antipyretics were prescribed, and a follow-up visit was scheduled for the next week. At the next visit the patient's fever and rash had gradually disappeared. The chest x-ray showed a small patchy infiltrate with micronodular shadows in the apical segment of the right upper lobe, but he denied having respiratory symptoms. A MEIA fourth-generation screening HIV test (to detect antigen and antibodies against HIV1/2) was reactive, with a negative Western blot (WB). Two weeks after initial presentation the patient developed a productive cough. The smear test was negative for acid-fast bacilli, and a sample was processed for tuberculosis culture. Twenty-five

[1]Área de Investigaciones Clínicas-Fundación Huésped, Buenos Aires, Argentina.
[2]Centro Nacional de Referencia para el SIDA, Universidad de Buenos Aires, Buenos Aires, Argentina.

days later the patient was completely asymptomatic, but a chest computed tomography scan showed a patchy interstitial peribronchial shadow with calcified nodules in the upper right lobe and calcified lymph nodes in the pretracheal retrocaval space. At the same time, the tuberculosis skin test was negative, and a new WB showed gp160 and p24 bands. Baseline HIV-RNA viral load (bDNA) and CD4 count were 62,679 copies/mL (4.79 $\log_{10}$) and 419 (25%) cells/μL, respectively. At 38 days after the beginning of TB symptoms and sputum collection (53 days after the first evaluation at the emergency department), the sputum culture developed *Mycobacterium tuberculosis* that was sensitive to first-line drugs. That same day, the patient started 9 months of conventional treatment for TB, which was completed successfully. While on TB treatment, he maintained a consistently low viral load and high CD4 counts, and therefore antiretroviral therapy was not initiated. In June 2009, with a CD4 count of 357 cells/mm³, the patient started HAART, which he continues today. He has remained asymptomatic since then, and his recent laboratory values are viral load <50 copies/mL, and CD4 count 481 cells/mm³.

Percentages of Tregs were determined by peripheral blood flow cytometry using anti FoxP3, CD25, and CD4 antibodies as previously described (6). Initially (concomitantly with HIV seroconversion and the development of TB symptoms), the frequency of Tregs was higher and decreased over time. Concurrently, the proliferation *in vitro* of peripheral blood mononuclear cells to *M. tuberculosis* H37Rv strain [determined using the CFSE dilution method as described elsewhere (7)] was undetectable, although it showed a transitory increase after starting TB treatment (Fig. 1). The expression of CD38 and HLA-DR molecules on CD4 and CD8 cells remained high throughout follow-up, especially on CD8 T-lymphocytes (the median percentage of CD8+CD38+HLA-DR cells was 34%).

Our patient had a well-documented acute HIV infection. In addition, the clinical course of tuberculosis, the anatomic localization, and the radiology support the diagnosis of post-primary TB rather than a new infection.

Our patient is interesting for two reasons: (1) to the best of our knowledge, this patient is the first reported case of acute HIV infection and concomitant pulmonary TB; (2) in this patient we could detect initial high levels of Treg cells, which normalized after TB treatment. Although speculative, it seems plausible that immune dysregulation during acute HIV infection, in particular upregulation of Treg cells, may have contributed to a tolerant state (i.e., a negative TST and low proliferative responses to *M. tuberculosis* despite relatively preserved CD4 counts) that may have favored the reactivation of TB.

Conclusions

This case underlines the need to explore the role of Tregs, both in HIV-TB co-infected patients, and in the small subset
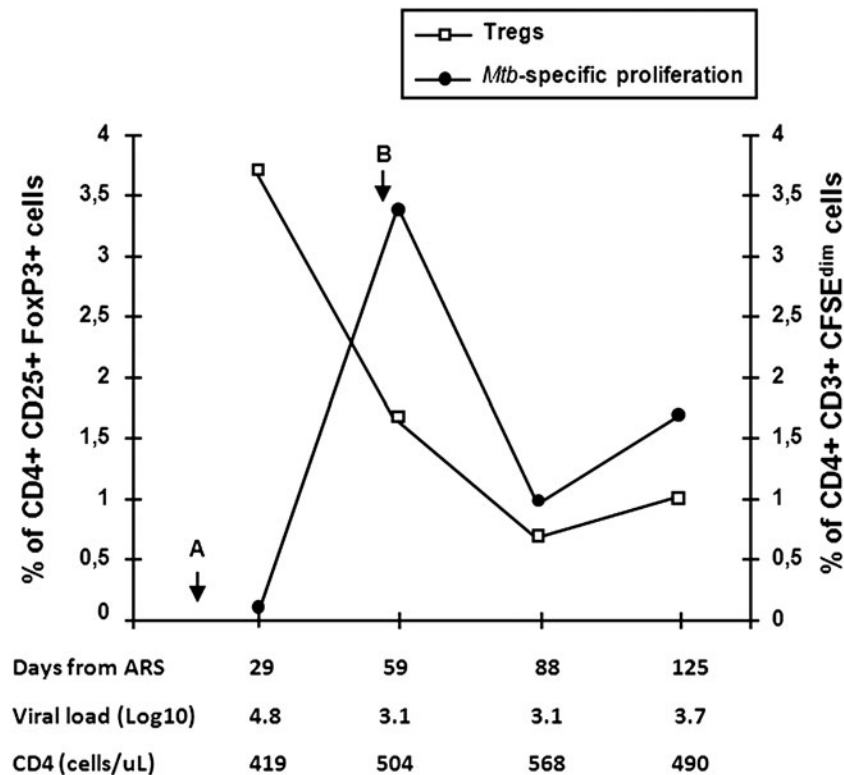

FIG. 1. Frequency of Treg lymphocytes and proliferation responses to *M. tuberculosis*. Percentages of Treg lymphocytes were determined in peripheral blood by flow cytometry using anti-FoxP3, CD25, and CD4 antibodies. The proliferation of peripheral blood mononuclear cells to the *M. tuberculosis* H37Rv strain was determined *in vitro* in CD3+CD4+ lymphocytes using the CFSE dilution method. Tregs, MTB-specific proliferation, viral load (b-DNA), and CD4 count (flow cytometry) are shown for each follow-up sample (ARS, acute antiretroviral syndrome; arrow A indicates sputum collection, and arrow B initiation of TB treatment).

of HIV patients who develop opportunistic infections during the acute phase of infection.

Patient Consent and Ethical Committee

This patient, who is participating in the Argentinean HIV seroconverters cohort "Grupo Argentino de Seroconversion (Site Fundación Huésped)," has read and signed the informed consent form for this cohort. In addition, the patient signed a specific consent form to publish this article.

Author Disclosure Statement

No competing financial interests exist.

Authors' Contributions

O.S. conceived of the study and drafted the manuscript, M.F.Q. participated in the study design and carried out immunological studies, M.E.S. followed the patient and collected samples, G.T. participated in the immunological studies, and H.S. and P.C. participated in the coordination, analysis, and interpretation of the data. All authors read and approved the final manuscript.

Author Information

Omar Sued is currently working as regional advisor in HIV treatment and care at the Pan American Health Organization, Washington, D.C.

Acknowledgments

References

1. Cadogan M, and Dalgleish AG: HIV immunopathogenesis and strategies for intervention. Lancet Infect Dis 2008;8:675–684.
2. Sued O, Miro JM, Alquezar A, et al.: Primary human immunodeficiency virus type 1 infection: clinical, virological and immuological Microbiol Clin 2006;24:238–244.
3. Lillie PJ, Barlow GD, Moss PJ, Parsonage MJ, Adams K, and Thaker HK: HIV seroconversion complicated by *Mycobacterium kansasii* infection. AIDS 2007;21:650–652.
4. Holmes D, Jiang Q, Zhang L, and Su L: Foxp3 and Treg cells in HIV-1 infection and immuno-pathogenesis. Immunol Res 2008;41:248–266.
5. Jiang Q, Zhang L, Wang R, et al.: FoxP3+CD4+ regulatory T cells play an important role in acute HIV-1 infection in humanized Rag2-/-gammaC-/- mice *in vivo*. Blood 2008;112:2858–2868.
6. Hougardy JM, Place S, Hildebrand M, Drowart A, Debrie AS, Locht C, and Mascart F: Regulatory T cells depress immune responses to protective antigens in active tuberculosis. Am J Respir Crit Care Med 2007;176:409–416.
7. Chen X, Zhou B, Li M, et al.: CD4(+)CD25(+)FoxP3(+) regulatory T cells suppress *Mycobacterium tuberculosis* immunity in patients with active disease. Clin Immunol 2007;123:50–59.
8. Geldmacher C, Schuetz A, Ngwenyama N, et al.: Early depletion of *Mycobacterium tuberculosis*-specific T helper 1 cell responses after HIV-1 infection. J Infect Dis 2008;198:1590–1598.
9. Bronke C, Palmer NM, Westerlaken GH, et al.: Direct *ex vivo* detection of HLA-DR3-restricted cytomegalovirus- and *Mycobacterium tuberculosis*-specific CD4+ T cells. Hum Immunol 2005;66:950–961.

Address correspondence to:
Dr. Pedro Cahn
Fundación Huésped
Área de Investigaciones Clínicas
Calle Angel Peluffo 3932 (C1202ABB)
Buenos Aires, Argentina

E-mail: pcahn@huesped.org.ar