CD-4/CD-8 lymphocytopenia in HIV negative patients with severe, chronic granulomatous infections

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Abstract

Background: *CD-4 lymphocytopenia can occur in acquired immunodeficiency syndrome (AIDS), in severe combined immunodeficiency, with the use of corticosteroids and/or immunosuppressive drugs, and in patients with idiopathic CD-4 lymphocytopenia. The mechanism for the lymphocytopenia is different in each of these illnesses.*

Objective: *Description of HIV-negative patients with severe disseminated tuberculosis or coccidioidomycosis and lymphocytopenia.*

Settings and patients: *All patients were referred to a University Medical Center in Northwest Texas, USA. Four had disseminated tuberculosis, and three had disseminated coccidioidomycosis.*

Main outcome measures: *Follow-up of lymphocyte subset counts and clinical improvement with the treatment of the underlying granulomatous infection.*

Results: *Five patients had an increase in both CD-4 and CD-8 lymphocyte subset counts with treatment of the underlying granulomatous infection. All patients had clinical improvement with initial therapy of the granulomatous infection. One patient succumbed to disseminated tuberculosis (meningitis) and two to disseminated coccidioidomycosis. One patient was lost to follow up.*

Conclusions: *We report a group of HIV-negative patients who had CD-4 lymphocytopenia in response to severe, disseminated, chronic granulomatous infections. With the treatment of the granulomatous infection the lymphocytopenia improved. This finding, coupled with preserved CD-4/CD-8 ratios, can help to differentiate these patients from those with other causes of lymphocytopenia or AIDS.*

Key words: granulomatous infection, tuberculosis, lymphocytopenia, CD4-lymphocytes, coccidioidomycosis

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Introduction

CD-4 is a transmembrane glycoprotein found on T-helper lymphocytes, megakaryocytes, megakaryocyte precursors, erythroid precursors, and occasionally with small expression on other lymphocyte subsets. Human immunodeficiency virus (HIV) infects the T-helper lymphocyte by binding to the CD-4 molecule in association with co-receptors, such as chemokine receptors CCR5 or CXCR4. CD-4 lymphocytopenia is an indicator of advanced HIV infection but can also develop in inherited diseases, such as severe combined immunodeficiency, with the use of immunosuppressive drugs or corticosteroids, or in the rare condition of idiopathic CD-4 lymphocytopenia.[1-4]

We have identified a group of patients with unexplained CD-4 lymphocytopenia associated with severe disseminated tuberculosis or disseminated coccidioidomycosis. They all had low CD-4 and CD-8 counts with preserved CD-4/CD-8 ratios. The CD-4 counts improved with adequate treatment of the underlying granulomatous infections. Patients with low CD-4 counts and low CD-4/CD-8 ratios are susceptible to multiple opportunistic infections and malignancies. However, our patients had improvement of both CD-4 and CD-8 lymphocytopenia with the treatment of the granulomatous infection. These characteristics help differentiate these patients from other causes of CD-4 lymphocytopenia leading to opportunistic infections.

Methods

All patients were independently referred for evaluation and treatment of chronic granulomatous infections and CD-4 lymphocytopenia. All patients were seen at Texas Tech University Health Science Center and University Medical Center Hospital in Lubbock, TX.

HIV disease was excluded with a negative HIV-1 and HIV-2 enzyme immunoassay and Western blot assays. Some results were confirmed by multiple additional tests, including p24 antigen, HIV RNA by polymerase chain reaction (PCR), or HIV culture. None of the patients had a known immunodeficiency or had used immunosuppressive drugs or corticosteroids. HIV-1 and HIV-2 enzyme immunoassays (HIV-1/HIV-2 EIA kit, Abbot Laboratories, Abbott Park, IL) were performed according to established methods. Western Blot assays were sent to Quest Laboratory (California). HIV culture, p24 antigen, and HIV RNA PCR were sent to Nichols Institute (California). Lymphocyte immunophenotyping was performed by flow cytometry at our flow cytometry laboratory with the use of monoclonal antibody panels supplied by Coulter Corporation (Florida) with recommended techniques. The specimens were analyzed on the Coulter Epics XL flow cytometer.

We defined CD-4 lymphocytopenia as a CD-4 lymphocyte count fewer than 600 cells per mm3 (0.6 X 9^9 /L). We recognize that this number is above that used for the definition of AIDS. We defined an abnormal CD-4/CD-8 ratio as less than 1.2, the same definition as in HIV patients. Complete blood counts and blood chemistries were performed by standard methods

Patient results

Six men and one woman were identified (Table). Four men had disseminated tuberculosis, and two had disseminated coccidioidomycosis. The woman had severe disseminated coccidioidomycosis. The four patients with tuberculosis ranged in age from 45 to 54. One was Caucasian, and three were Mexican-American. The three patients with coccidioidomycosis were African Americans, with ages ranging from 18 to 44. All patients had negative HIV screening, negative Western Blot tests, and negative HIV RNA PCR. Patient #2 had an initial positive HIV screening test. However, repeat screening tests were negative as were all confirmatory tests. All patients had a reduced number of CD-4 lymphocytes and a reduced number of CD-8 lymphocytes which led to preserved CD-4/CD-8 lymphocyte ratios. Five patients had improvement in their lymphocytopenia with standard treatment of their underlying granulomatous disease. Two patients with coccidioidomycosis died; one patient with tuberculous meningitis also died. One patient was lost to follow up after starting treatment.

Table: CD-4 counts, CD-8 counts and CD4/CD8 ratios before and after treatment

		At Diagnosis			After Treatment		
No	Infection	CD4+ count cells/mm^3 *	CD8+ count cells/mm^3 *	CD4/CD8 ratio	CD4+ count cells/mm^3 *	CD8+ count cells/mm^3 *	CD4/CD8 ratio
1	Tuberculosis	216	72	3.00	415	124	3.35
2	Tuberculosis	82	N/A	N/A	560	289	1.75
3	Tuberculosis	245	78	3.15	558	250	2.23
4	Tuberculosis#	381	83	3.86	N/A	N/A	N/A
5	Coccidioidomycosis	591	222	2.67	793	404	1.96
6	Coccidioidomycosis	228	198	1.26	386	278	1.39
7	Coccidioidomycosis#	100	66	1.50	N/A	N/A	N/A

N/A - not available; * - 0.001 X I 109 /L ; # - died

Discussion

Patients with HIV disease have low CD-4 lymphocyte subset counts and reversed CD-4/CD-8 ratios that worsen as the viral infection progresses and the clinical condition progresses toward AIDS. With treatment of the HIV infection the lymphocytopenia may improve. These patients are subject to opportunistic infections and opportunistic malignancies. Idiopathic CD-4 lymphocytopenia is a rare condition with no cause for the immunodeficiency. Almost all of the patients reported had persistently reversed CD-4/CD-8 ratios. These patients are also susceptible to opportunistic disease and after the treatment of the opportunistic illness (if present) they continue to have lymphocytopenia and a reversed CD-4/CD-8 ratios.[1-4]

We did not control for diurnal variations of lymphocyte counts and subsets.[5] However, all of the lymphocyte counts were performed in the same laboratory using the same equipment and procedures. All of our patients with severe chronic granulomatous infections had CD-4 and CD-8 lymphocytopenia but normal CD-4/CD-8 ratios. Their lymphocytopenia improved with treatment of the underlying illness. Thus, our patients differ from those with advanced HIV infection, patients having lymphocytopenia due to other illnesses or drugs, and those with idiopathic CD-4 lymphocytopenia.

Similar findings have been reported in patients with tuberculosis, histoplasmosis, and other fungal infections. Other authors have reported CD-4 lymphocytopenia in a wide variety of infectious and non-infectious illnesses.[5-10] There is one case report of profound T-lymphocytopenia in a dual infection with tuberculosis and Cryptococcus.[11] Patients with severe tuberculosis and lymphocytopenia have recently been reported to have improvement in the lymphocyte counts with adequate treatment.[12-13] However, the finding of disseminated tuberculosis coupled with lymphocytopenia indicates a poor prognosis.[14]

There are multiple hypotheses for the cause of the lymphocytopenia in tuberculosis.[15-20] These range from “sequestration” to lymphocytopenia due to a catabolic state. Tuberculous infected macrophages secrete several inflammatory cytokines and may stimulate accessory cells, such as endothelial cells, to secrete additional inflammatory cytokines.[15] A combination of these cytokines can stimulate or suppress lymphocyte blastogenesis. Recent in vitro studies have shown that M. tuberculosis affects monocyte-derived dendritic cells. This may down

regulate the T helper response to infection.[18-22] Immunosuppression in tuberculosis may also be associated with increases and decreases of multiple growth factors. [23] Other viral infections may cause lymphocytopenia. [24-25]

Conclusion

In conclusion, we report a group of HIV-negative patients who have CD-4 and CD-8 lymphocytopenia in response to severe, disseminated, chronic granulomatous infections. With treatment of the granulomatous infections the lymphocytopenia improved. This finding coupled with preserved CD-4/CD-8 ratios can help differentiate these patients from those with other causes of lymphocytopenia and AIDS.

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