CLINICAL AND LABORATORY PROFILE OF PATIENTS WITH IDIOPATHIC CD4 LYMPHOCYTOPENIA- A RARE CLINICAL ENTITY

Vijayashree Thyagaraj[1], Karthik Ashok[2]

[1]Associate Professor, Department of Medicine, M. S. Ramaiah Medical College and Hospital, Bangalore.
[2]Assistant Professor, Department of Medicine, M. S. Ramaiah Medical College and Hospital, Bangalore.

ABSTRACT

BACKGROUND

Since 1989, several investigators have reported unusual cases of severe opportunistic infections associated with CD4 lymphocytopenia in the absence of human immunodeficiency virus infection. The cause of this condition is unknown. The Centres for Disease Control and Prevention (CDC) defines Idiopathic CD4 T Lymphocytopenia (ICL) as a clinical condition in which patients with depressed numbers of circulating CD4+ T-cell lymphocytes (<300 cells/μL or <20% of total T cells) at a minimum of two separate time points at least 6 weeks apart, have no laboratory evidence of infection with human HIV-1 or HIV-2, or any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells.

The aim of the study is to analyse the clinical profile, opportunistic infections, laboratory parameters and outcome in terms of survival of patients diagnosed with ICL.

MATERIALS AND METHODS

Eight HIV negative patients who presented with opportunistic infections and who were diagnosed with ICL from 2007 to 2015 were included in the study. A detailed history was taken; physical examination was performed and the nature of illness with which they presented was documented. Then, CD4 and CD8 counts were done and CD4 count was repeated after a 6-week interval. The patients were followed up until discharge or death.

RESULTS

The mean age was 37.50±9.55 years. There were six males (75%) and two females (25%). Fever was a presenting symptom among six (75%) of them. Two were diagnosed to have cutaneous cryptococcosis (25%), two with invasive aspergillosis (25%) and four with tuberculosis (50%). Absolute lymphocyte count was less than 1200 in seven patients (87.5%), which roughly correlates with a CD4 count of less than 200 cells/μL, among PLWHIV. The mean CD4 count was 183.63±63.74 cells/μL during the first measurement and 214.43±103.98 cells/μL during the second one. Two patients died (37.5%). None of the patients were recorded to have any form of malignancy.

CONCLUSION

ICL mostly affects young individuals with unusual opportunistic infections, the most common being tuberculosis and cryptococcosis. There was no worsening of the CD4 count with time and death in our patients was not directly related to the condition.

KEYWORDS

Idiopathic CD4 Lymphocytopenia, Non-HIV, CD4 Count, Opportunistic Infections.

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BACKGROUND

Though ICL was first described more than two decades ago, there still remains a lot that is unknown about this condition. Its aetiology is unknown; pathogenesis is still unclear and there is no specific therapy for it. There is no data to support involvement of an infectious agent. Suppression of cell-mediated immunity by infectious agents other than HIV can occur, yet the full role of lymphocytic subgroups in both conventional and opportunistic infections is not fully understood.[1] Idiopathic CD4 lymphocytopenia differs from HIV infection in its immunologic characteristics and its non-progression over time. The clinical spectrum of ICL ranges from an asymptomatic laboratory abnormality to life-threatening opportunistic infections and certain malignancies.

This condition is also extremely rare. A recent study conducted found that there were 259 cases of ICL reported worldwide since 1989.[2]

The one common feature is the reduced circulating CD4+ T cell count, which may be due to a decreased production, increased destruction, tissue sequestration or any combination of these.[3] A genetic role in the form of

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Corresponding Author:
Dr. Vijayashree Thyagaraj,
No. 2035, Sobha Chrysanthemum Thanisandra,
Main Road, Near Nagawara Signal,
Bangalore-560077.
E-mail: vijadisudha@gmail.com
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decreased bone marrow clonogenic capability with diminished stem cell precursors contributing to CD4 depletion has been described.[4] Another important substance in the maintenance of the peripheral CD4+ T cell count is p56 kinase activity. A disturbed thymic T-cell maturation may also have a role.

There may be an increased apoptotic depletion of CD4+ T cells associated with over expression of the Fas/CD95 and Fas ligand.[5] A high serum level of IL-7 may be seen in these patients with a blunted T-cell response.[3] Chemokine receptors CXCR4 expression was found to be low in patients with ICL and this was restored after administering IL-2 in some patients.

The differential diagnosis for ICL includes infections such as HIV 1 and 2, HTLV 1 and 2, mycobacterial infection, EBV and CMV infections. Malignancies such as lymphoma, autoimmune disorders such as SLE, Sjogren's syndrome, administration of chemotherapeutic medications, immunosuppressants and some genetic conditions are other differential diagnosis.[3]

Therapy for this condition involves the treatment of the presenting infection and prophylaxis against opportunistic infections, guidelines for which still come from studies done on HIV infected patients. Dead vaccines maybe given while live vaccines are contraindicated.[6]

A few investigators reported successful treatment with IL-2 for opportunistic infection associated with ICL. The idea of IL-2 came from its use in HIV patients with CD4+ T lymphopenia. Interleukin-2 has showed significant increase in CD4 counts and possible clinical improvement in immunological function. Limited data from those reports support IL-2 as a relatively safe and potentially effective treatment for ICL patients with opportunistic infections, especially when combined with conventional treatment regimens. Another group of investigators have studied the use of IL-7 in increasing the CD4 cell count in these patients and have shown promising results.[7] Even haematopoietic stem cell transplantation has been tried successfully in some patients.[8,9]

MATERIALS AND METHODS

Eight HIV negative patients who presented with opportunistic infections were included in this observational clinical study from 2007 to 2015 after informed consent. A detailed history was taken and physical examination was performed on each of these patients. Immediate family members were interviewed for their medical history as well. Thereafter, patients underwent testing for antibodies to HIV 1 and 2 by ELISA method. Consequently, CD4 and CD8 counts were done and CD4 count was repeated after a 6-week interval. Other important laboratory parameters such as complete blood counts, liver function tests, renal function tests, RBS and tests related to autoimmunity such as ANA and ANCA were also done. The course in the hospital was monitored until discharge or death.

Statistical analysis was done using SPSS 20.0 version. Descriptive statistics such as mean, standard deviation and percentage was used.

RESULTS

Most patients studied were in the 3rd or 4th decade of life. The mean age was 37.50±9.55 years. There were six male (75%) and two female (25%) patients. Six patients were married (75%) and two (25%) were single. Most subjects interviewed had no risk for development of HIV infection (87.5%). Seven patients (87.5%) had no other comorbid conditions. One patient had pre-existing rheumatoid arthritis, but was not on corticosteroids. Fever was a presenting symptom among six (75%) of them. Two patients (25%) appeared emaciated on presentation. On admission to hospital, two were diagnosed to have cutaneous cryptococcosis (25%), two with invasive aspergillosis (25%) and four with tuberculosis (50%) (Table 1). Most complications that occurred during hospital stay were treatment related such as adverse reactions to amphotericin and drug-induced hepatitis. Two patients died (37.5%), one due to pulmonary thromboembolism and another due to upper GI bleed secondary to oesophageal varices. One patient left against medical advice (12.5%).

Three patients (37.5%) were anaemic with mean haemoglobin of all the patients being 11.06±3.43 gm/dL. The same number (37.5%, n=3) had a total count less than or equal to 4000 cells/cumm with a neutrophilic predominance. The mean total leucocyte count was 7767.50±32 cells/cumm. The absolute lymphocyte count was less than 1200 in seven patients (87.5%), which roughly correlates with a CD4 count of less than 200 cells/μL cells among PLWHIV (Table 2). Four patients (50%) had thrombocytopenia at presentation with mean platelet count being 0.81 lakh/cumm. Four patients (50%) had a CD4 count of less than 200 cells/μL at presentation. The mean CD4 count was 183.63±63.74 cells/μL during the first measurement and 214.43±103.98 cells/μL during the second one (Table 3). The CD4/CD8 ratio was less than one among five patients (62.5%) and more than one among three (37.5%) of them (Table 4).

Antibodies to HIV 1 and 2 were negative in all patients. None of the patients tested positive for either hepatitis B or C. Serological testing for ANA and ANCA wherever it was done was negative.

Clinical Diagnosis	No. of patients	%
Cutaneous cryptococcosis	2	25.0
Invasive pulmonary aspergillosis	2	25.0
TB	4	50.0
Total	**8**	**100.0**

Table 1. Distribution of Clinical Diagnosis Among Patients Studied

	Number of Patients (n=8)	%	Mean±SD
Absolute lymphocyte count			
<1200	7	87.5	767.88±628.61
>1200	1	12.5	

Table 2. Absolute Lymphocyte Count of Patients Studied

CD4 Count	Number of Patients (n=8)	%	Mean±SD
1st			
<200	2	25.0	183.63±63.74
>200	6	75.0	
2nd			
<200	2	25.0	214.43±103.98
>200	5	75.0	

Table 3. CD4 Count

	Number of Patients (n=8)	%	Mean±SD
CD8			
<150	1	12.5	252.25±137.86
>150	7	87.5	
CD4/CD8			
<1	5	62.5	0.85±0.43
>1	3	37.5	

Table 4. CD8 and CD4/CD8

DISCUSSION

In our study, there was a male preponderance (75%) to the disease. This was similar to findings from a study, which analysed comprehensive data from 258 cases collected from 143 published papers where they found that men constituted 62% of the study population.[2]

The mean age of our patients was 37.50±9.55 years. The mean age at diagnosis of first opportunistic infection (or ICL if no opportunistic infection was reported) was 40.7±19.2 years in another study as well.[2] The mean age was 43 years in another study done on 47 patients by Smith DK, Neal JJ and Holmberg SD.[10]

None of the subjects except one had a high-risk behaviour predisposing to sexually transmitted diseases though some studies reported such an occurrence.[10,2]

The most common infection encountered was tuberculosis (50%, n=4), followed by cutaneous cryptococcosis in two (25%) and invasive aspergillosis in two (25%) individuals. Three out of four subjects with tuberculosis had an extrapulmonary or a disseminated form while one patient had pulmonary Kochs. Even in other studies, it was found that cryptococcal infections and nontuberculous mycobacterial infections were the major presenting opportunistic infections of ICL.[3,2,11] One patient presented with multiple opportunistic infections in the past. A study by Ahmed D S et al in 2013 reported the incidence of repeated opportunistic infections to the tune of 32.9%.[2]

Other infections in our patients included cutaneous histoplasmosis and oral candidiasis, which occurred together in one patient.

Six subjects had anaemia and an equal number had leucopenia. Three subjects had thrombocytopenia. There are no large studies reporting leucopenia or thrombocytopenia in the initial screening tests. The absolute lymphocyte count was less than 1200 among seven (87.5%) of them. An absolute lymphocyte count of less than 1200 is often taken as a surrogate marker of a CD4 count of less than 200 cells/μL. Most patients in another study too had an absolute lymphocyte count of less than 1200.[11] In a recently done study, 5 out of 304 (1.65%) seronegative haemophilic men had persistent lymphocytopenia (<1200 total lymphocytes) even in the follow up period.[12] The mean CD4 count was 183.63 cells/μL in our study. It was 214.43±103.98 cells/μL during the second round of testing after 6 weeks. The mean initial CD4 count in another large study analysis was 142.6±103.9 cells/μL. The mean CD8 count was 252.25±137.86 in our study compared to 295±273.6 cells/μL in another study.[2] In a study involving the follow up of 40 ICL patients, at the time of diagnosis, the mean cell counts were as follows- mean CD4 count- 127 cells/μL mean CD8- 236 cells/μL.[11]

The CD4/CD8 was less than one in five subjects and more than one among three of them. The mean CD4/CD8 was 0.85±0.43 in our study. The mean initial CD4:CD8 ratio was 0.6±0.7 in another study.[11]

Two patients in our study died due to unrelated causes and not due to the opportunistic infections. The mean CD4 count in the patients who died was 175 cells/μL. In a prospective study, a mean CD4 T-cell count <150 cells/μL and NK cell count <100/mm were predictors of death.[11] Some studies have reported association of malignant conditions and ICL.[1,11] However, none of our patients had any form of malignancy. CD8 T lymphocytopenia (<180/mm) and the degree of CD4 T cell activation at presentation were associated with adverse outcome (opportunistic infection-related death; P=0.003 and 0.02, respectively) in another study.[13]

CONCLUSION

There have been reports of ICL in the medical literature since the late 1980s. Though being a rare disease, it has been encountered by clinicians on and off. The condition is suspected whenever a person presents with unusual and unexplained opportunistic infections. The most important differential diagnosis of ICL is HIV infection. Despite these similarities, ICL seems to be more common in young people often with no high-risk behaviour. The most common opportunistic infections appear to be tuberculosis and cryptococcosis. There does not seem to be a progressive decline in the CD4 counts. The treatment and its success of the underlying problem is still experimental and anecdotal. Various novel therapies have been tried with success in other countries. No specific treatment for this condition has been tried as yet in India.

ABBREVIATIONS

ICL- Idiopathic CD4 T Lymphocytopenia.
PLWHIV- People Living with HIV.
ALC- Absolute Lymphocyte Count.

REFERENCES

[1] Gholamin M, Bazi A, Abbaszadegan MR. Idiopathic lymphocytopenia. Curr Opin Hematol 2015;22(1):46-52.

[2] Ahmad DS, Esmadi M, Steinmann WC. Idiopathic CD4 Lymphocytopenia: spectrum of opportunistic infections, malignancies, and autoimmune diseases. Avicenna J Med 2013;3(2):37-47.

[3] Zonios D, Sheikh V, Sereti I. Idiopathic CD4 lymphocytopenia: a case of missing, wandering or ineffective T cells. Arthritis Res Ther 2012;14(4):222.

[4] Isgrò A, Sirianni MC, Gramiccioni C, et al. Idiopathic CD4+ lymphocytopenia may be due to decreased bone marrow clonogenic capability. Int Arch Allergy Immunol 2005;136(4):379-384.

[5] Roger PM, Bernard-Pomier G, Counillon E, et al. Overexpression of Fas/CD95 and Fas-induced apoptosis in a patient with idiopathic CD4+ T lymphocytopenia. Clin Infect Dis 1999;28(5):1012-1016.

[6] Walker UA, Warnatz K. Idiopathic CD4 lymphocytopenia. Curr Opin Rheumatol 2006;18(4):389-395.

[7] Sheikh V, Porter BO, DerSimonian R, et al. Administration of interleukin-7 increases CD4 T cells in idiopathic CD4 lymphocytopenia. Blood 2016;127(8):977-988.

[8] Cervera C, Fernández-Avilés F, de la Calle-Martin O, et al. Non-myeloablative hematopoietic stem cell transplantation in the treatment of severe idiopathic CD4+ lymphocytopenia. Eur J Haematol 2011;87(1):87-91.

[9] Lum SH, Bonney D, Cheesman E, et al. Successful curative therapy with rituximab and allogeneic haematopoietic stem cell transplantation for MALT lymphoma associated with STK4-mutated CD4+ lymphocytopenia. Pediatr Blood Cancer 2016;63(9):1657-1659.

[10] Smith DK, Neal JJ, Holmberg SD. Unexplained opportunistic infections and CD4+ T-lymphocytopenia without HIV infection. An investigation of cases in the United States. The Centers for Disease Control Idiopathic CD4+ T-lymphocytopenia Task Force. N Engl J Med 1993;328(6):373-379.

[11] Régent A, Autran B, Carcelain G, et al. Idiopathic CD4 lymphocytopenia: clinical and immunologic characteristics and follow-up of 40 patients. Medicine (Baltimore) 2014;93(2):61-72.

[12] O'Brien TR, Diamondstone L, Fried MW, et al. Idiopathic CD4+ T-lymphocytopenia in HIV seronegative men with hemophilia and sex partners of HIV seropositive men. Multicenter Hemophilia Cohort Study. Am J Hematol 1995;49(3):201-206.

[13] Zonios DI, Falloon J, Bennett JE, et al. Idiopathic CD4+ lymphocytopenia: natural history and prognostic factors. Blood 2008;112(2):287-294.