Idiopathic CD4 Lymphocytopenia: Spectrum of opportunistic infections, malignancies, and autoimmune diseases

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ABSTRACT

Idiopathic CD4 lymphocytopenia (ICL) was first defined in 1992 by the US Centers for Disease Control and Prevention (CDC) as the repeated presence of a CD4+ T lymphocyte count of fewer than 300 cells per cubic millimeter or of less than 20% of total T cells with no evidence of human immunodeficiency virus (HIV) infection and no condition that might cause depressed CD4 counts. Most of our knowledge about ICL comes from scattered case reports. The aim of this study was to collect comprehensive data from the previously published cases to understand the characteristics of this rare condition. We searched the PubMed database and Science Direct for case reports since 1989 for Idiopathic CD4 lymphocytopenia cases. We found 258 cases diagnosed with ICL in 143 published papers. We collected data about age, sex, pathogens, site of infections, CD4 count, CD8 count, CD4:CD8 ratio, presence of HIV risk factors, malignancies, autoimmune diseases and whether the patients survived or died. The mean age at diagnosis of first opportunistic infection (or ICL if no opportunistic infection reported) was 40.7 ± 19.2 years (standard deviation), with a range of 1 to 85. One-sixty (62%) patients were males, 91 (35.2%) were females, and 7 (2.7%) patients were not identified whether males or females. Risk factors for HIV were documented in 36 (13.9%) patients. The mean initial CD4 count was $142.6 \pm 103.9/\text{mm}^3$ (standard deviation). The mean initial CD8 count was $295 \pm 273.6/\text{mm}^3$ (standard deviation). The mean initial CD4:CD8 ratio was 0.6 ± 0.7 (standard deviation). The mean lowest CD4 count was $115.4 \pm 87.1/\text{mm}^3$ (standard deviation). The majority of patients 226 (87.6%) had at least one infection. Cryptococcal infections were the most prevalent infections in ICL patients (26.6%), followed by mycobacterial infections (17%), candidal infections (16.2%), and VZV infections (13.1%). Malignancies were reported in 47 (18.1%) patients. Autoimmune diseases were reported in 37 (14.2%) patients.

Key words: Autoimmune diseases, idiopathic CD4 lymphocytopenia, lymphopenia, opportunistic infections

INTRODUCTION

A 41-year-old female was seen in our Infectious Disease clinic in 2007. She was diagnosed with cutaneous and lymphadenomatous cryptococcal disease in 1995 and subsequently ICL. She has been on only fluconazole 200 mg daily as prophylaxis ever since. She had no recurrence of cryptococcal infections. In 2003, she had an episode of chickenpox and she has been suffering from atopic dermatitis since childhood. Her CD4 count was $64/\text{mm}^3$,

CD8 count $410/\text{mm}^3$, and CD4:CD8 0.15. She remained free of infections on follow up. She did not develop any autoimmune diseases or shingles.

Idiopathic CD4 lymphocytopenia (ICL) was first defined in 1992 by the US Centers for Disease Control and Prevention (CDC) as the repeated presence of a CD4+ T-lymphocyte count of fewer than 300 cells per cubic millimeter or of less than 20% of total T cells with no evidence of human immunodeficiency virus (HIV) infection and no condition

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that might cause depressed CD4 counts. Several cases were reported since 1989 with patients having opportunistic infections in the setting of persistent low CD4 counts without HIV infection. This led the CDC in 1992 to launch a survey in an attempt to characterize this newly evolving entity. The CDC Idiopathic CD4 Lymphocytopenia Task Force reviewed 230,129 cases in the Centers for CDC AIDS Reporting System and found 47 patients to meet the CDC criteria of ICL. Among these 47 patients, 40% had AIDS-defining illnesses, 53% had conditions that were not AIDS-defining, and 6% were asymptomatic. The investigation indicated that ICL is a rare entity with no evidence of transmissible agent since the cases were not clustered and the contacts of the patients had no immunodeficiency.^[1]

Most of our knowledge about the associated conditions with ICL comes from case reports due to rarity of this condition. A prospective study done by NIH followed 39 ICL patients between 1992 and 2006 to understand the natural history, clinical course, CD4 T lymphocyte kinetics, outcome, and prognostic factors of ICL. Seven patients presented with no infection. Cryptococcal and non-tuberculous mycobacterial infections were the main presenting opportunistic infections. In 32 patients, CD4 T-cell counts remained less than 300/mm³ and in 7 patients normalized after an average of 31 months. Fifteen (41.6%) developed an opportunistic infection in follow-up, 5 (13.8%) of which were "AIDS-defining clinical conditions," and 4 (11.1%) developed autoimmune diseases. Seven patients died, 4 from ICL-related opportunistic infections.^[2]

The aim of this review was to collect the previously published ICL cases to study its different important aspects. The main studied aspects were age, sex, CD4 count, CD8 count, CD4:CD8 ratio, presence of HIV risk factors, opportunistic infections, malignancies, autoimmune diseases and whether the patients survived or died.

MATERIALS AND METHODS

We searched the PubMed database and ScienceDirect for case reports from 1989 to April 2012 using the following keywords: CD4 lymphocytopenia, idiopathic CD4, Idiopathic CD4 lymphocytopenia, ICL, opportunistic infections, Kaposi, TB, mycobacterium, nocardia, PCP, JCV, cryptococcus, CMV, herpes, candida, HPV, and VZV. These were used in various combinations using AND with OR as modifiers. References identified were supplemented with relevant citations from the reference lists of the consulted papers. Only English language papers were reviewed. We found 258 cases diagnosed with ICL in 143 published papers^[1,3-145] out of 254 articles found by search. All cases

included in this review were diagnosed and published as cases of ICL with negative HIV testing. Negative HIV testing was by ELISA, western blot or PCR. However, we collected only how many patients had negative PCR testing.

We collected data about age, sex, pathogens, site of infections, CD4 count, CD8 count, CD4:CD8 ratio, presence of HIV risk factors, malignancies, autoimmune diseases and whether the patients survived or died. Absolute numbers and percentages were calculated. We included our case to the previously published cases. Therefore, the total number of cases became 259. Cases that were present in more than one article were included once in our review.

RESULTS

The mean age at diagnosis of first opportunistic infection (or ICL if no opportunistic infection reported) was 40.7 ± 19.2 years (standard deviation), with a range of 1 to 85. One patient with ICL was reported to have candidal infections since birth.^[43] The oldest patient with ICL was 85 years-old.^[22] One-sixty (62%) patients were males, 91 (35.2%) were females, and 7 (2.7%) patients were not identified whether males or females. Four patients had a family member with low CD4 counts.^[7,12,51,54] Risk factors for HIV were documented in 36 (13.9%) patients, while 119 (46.1%) patients had no risk factors. Documentation was lacking for HIV risk factors in 103 (40%). All patients had some sort of negative HIV test, but PCR was done in 75 (29%) patients. The rest of the patients, 183 (71%), had no documentation of whether HIV PCR was done or not. Table 1 shows the general descriptive frequencies of different variables in all ICL patients.

The mean initial CD4 count was 142.6 ± 103.8 /mm³ (standard deviation). The mean initial CD8 count was 295 ± 273.6 /mm³ (standard deviation). The mean initial CD4:CD8 ratio was 0.6 ± 0.7 (standard deviation). The mean lowest CD4 count was 115.4 ± 87.1 /mm³ (standard deviation). The mean of the latest reported CD4 count on follow up was 193.2 ± 155.7 /mm³ (standard deviation). CD4 count recovered at some point on follow up to above 300/mm³ in 27 (10.4%) patients. Twenty-four patients died due to their opportunistic infections. Two-hundred patients (77.5%) survived their presenting illness, whether OI, malignancy, or autoimmune disease. The outcome was not documented in 34 (13.2%) patients.

The majority of patients, 226 (87.6%), had at least one opportunistic infection. Eighty-five (32.9%) patients had multiple opportunistic infections. A very few number of infections were detected on autopsies.^[23,98]

Figure 1 shows the most common 10 infections in ICL patients and their percentages. Cryptococcal infections were the most common 69 (26.6%) in ICL patients. Meningitis was the most common cryptococcal infection followed by pneumonia and then osteomyelitis. Candidal infections were reported in 42 (16.2%) patients. The mouth was the most common site for candidiasis followed by the esophagus.

Table 1: Frequencies of different variables in all ICL patients

Age	Mean: 40.7 years SD: 19.2
M:F	Males: 160 (62) Females: 91 (35.2) Not specified: 7 (2.7)
HIV risk factors	Yes: 36 (13.9) No: 119 (46.1) Not specified: 103 (40)
HIV PCR	Done: 75 (29) 226 (87.6)
Patients who had opportunistic infection(s)	
Patients who had cancers	47 (18.1)
Patients who had autoimmune disease(s)	37 (14.2)
Patients who had multiple opportunistic infections	85 (32.9)
Patients who had multiple cancers	15 (5.8)
Outcome	Died due to OI: 24 (9.3) Survived at time of diagnosis: 200 (77.5) Not specified: 34 (13.2)
Lowest CD4 count	Mean 115.4/mm ³ SD 87.1
Initial CD4 count	Mean 142.6/mm ³ SD 103.8
Initial CD8 count	Mean 295/mm ³ SD 273.6
Initial CD4:CD8 ratio	Mean 0.6/mm ³ SD 0.7
Latest reported CD4 count on follow up	Mean 193.2/mm ³ SD 155.7
SD: Standard deviation, OI: Opportunistic infection, ICL: Idiopathic CD4 lymphocytopenia, Figures in paranthesis are percentages	

Twenty (7.7%) patients had *Pneumocystis pneumonia* (PCP). Eight patients had infection with histoplasma. Table 2 shows the different fungal infections in ICL patients with the most commonly reported sites of infection.

Varicella zoster virus was the most common viral infection in ICL patients 34 (13.1%), followed by human papilloma virus 30 (11.6%), herpes simplex virus 21(8.1%), and cytomegalovirus 15 (5.8%). The retina was the most commonly affected site by CMV. Other reported CMV infections included disseminated CMV infections and CMV esophagitis. Table 3 shows the different viral infections in ICL patients. Forty-four (17%) patients had mycobacterial infections. *Mycobacterium tuberculosis* was reported in 19 patients. Of these 19 patients, 17 had pneumonia, one patient had colitis, and another patient had UTI. *Mycobacterium avium* complex was reported in 17 patients. Of these 17 patients, 9 had pneumonia. Table 4 shows the different mycobacterial infections in ICL patients.

Table 2: Distribution of fungal infections in ICL patients (number)

Fungal infections	Number
Candidal infections	42
Oral	20
Esophagitis	10
Pneumonia	3
Vaginal	5
<i>Cryptococcus neoformans</i>	69
Meningitis	51
Pneumonia	17
Osteomyelitis	7
<i>Pneumocystis pneumonia</i>	20
Histoplasmosis	8
Aspergillosis	3
Blastomycosis	1
<i>Encephalitozoon cuniculi</i>	1
<i>Exophiala jeanselmei</i>	1
ICL: Idiopathic CD4 lymphocytopenia

Figure 1: The most common 10 infections in idiopathic CD4 lymphocytopenia patients and their percentages

Table 3: Distribution of viral infections in ICL patients (number)

Viral Infection	Number
Varicella zoster virus	34
Shingles	26
Disseminated infection	4
Chickenpox only	3
Human papilloma virus	30
Herpes simplex virus 1 and 2	21
Cytomegalovirus	15
Retinitis	5
JC virus	10
Molluscum contagiosum	8
Human herpesvirus 8	7
Epstein-Barr virus	5
Parvovirus B19	1

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Table 4: Distribution of mycobacterial infections in ICL patients (number)

Mycobacterial infections	44
<i>Mycobacterium tuberculosis</i>	19
Pneumonia	17
Disseminated	2
<i>Mycobacterium avium</i> complex	17
Pneumonia	9
Disseminated	8
<i>Mycobacterium chelonae</i>	3
Pneumonia	2
Skin	1
<i>Mycobacterium kansasii</i>	1
Pneumonia	1
<i>Mycobacterium mucogenicum</i>	1
Disseminated	1
<i>Mycobacterium xenopi</i>	1
Pneumonia	1
Atypical mycobacterium	2
Not specified	2

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Unusual bacterial infections included *Nocardia* spp, *Actinomyces* spp, *Fusobacterium nucleatum*, and *Rhodococcus equi*. Protozoal infections were reported in 11 patients. Eight patients had toxoplasmosis. Table 5 shows the different unusual bacterial and protozoal infections reported in ICL patients.

Thirty-seven patients (14.2 %) had autoimmune disease(s). Sjogren's disease was the most common reported autoimmune diseases in ICL patients ($n = 8$), followed by sarcoidosis ($n = 7$), and psoriasis ($n = 7$). Table 6 shows the autoimmune diseases reported in ICL patients. Eczema was reported in five patients, and one patient was reported with allergic rhinitis. Forty-seven (18.1%) patients had malignancies. Lymphoma with its subtypes, in general, was the most common malignancy in ICL patients. Squamous cell carcinoma of the skin is the second most common malignancy ($n = 9$), followed by

Table 5: Distribution of unusual bacterial and protozoal infections in ICL patients (number)

	Number
Bacterial infections	
<i>Salmonella</i> spp	3
Enteritis	
<i>Nocardia</i> spp	2
Cerebral abscess	1
Disseminated	1
<i>Fusobacterium nucleatum</i>	1
Hepatic abscess	
<i>Rhodococcus equi</i>	1
<i>Actinomyces</i> spp	1
Perianal abscess	
<i>Corynebacterium jeikei</i>	1
Pneumonia	
<i>Shigella</i> spp	1
Enteritis	
<i>Mycoplasma fermentans</i>	1
Disseminated	
Protozoal infections	
Toxoplasmosis	8
Cerebral	7
Disseminated	1
Cryptosporidiosis	1
Visceral Leishmaniasis	1
Giardiasis	1

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Table 6: Distribution of autoimmune diseases in ICL patients (number)

Autoimmune diseases	Number
Sjogren disease	8
Sarcoidosis	7
Psoriasis	7
Auto immune hemolytic anemia	3
Idiopathic thrombocytopenic purpura	3
Systemic lupus erythematosus	2
Vasculitis	2
Raynaud's disease	2
Thrombotic thrombocytopenic purpura	1
Waldstrom hypergammaglobulinemic purpura	1
Hashimoto thyroiditis	1
Behçet's-like syndrome	1
Anti-phospholipid Ab	1
Alopecia areata	1
Vitiligo	1

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Kaposi's sarcoma ($n = 7$). Table 7 shows the malignancies reported in ICL patients.

DISCUSSION

Idiopathic CD4 lymphocytopenia is a very rare disease. Cases were reported from all over the world. There is no apparent predilection to one geographical area. Patients are usually diagnosed in the middle of their age. Of the 259 reviewed cases, the mean age was 40.7 years. Most patients were diagnosed upon development of opportunistic

Table 7: Distribution of malignancies in ICL patients (number)

Malignancies	Number
Squamous cell carcinoma of the skin	9
Kaposi's sarcoma	7
Basal cell carcinoma of the skin	6
Lymphoma (without details on subtype)	6
Bowen's disease	6
Non-Hodgkin's lymphoma	5
Vulvar intraepithelial neoplasia	3
Primary effusion lymphoma	2
Mycosis fungoides	2
Acute lymphoblastic leukemia	2
Bladder tumor	2
Cervical intraepithelial neoplasia	2
Non-small-cell lung carcinoma	1
B-cell none-Hodgkin lymphoma	1
Large B-cell lymphoma	1
Diffuse large B cell lymphoma in bladder then orbit	1
Primary leptomeningeal lymphoma	1
Gastric cancer	1
Prickle cell carcinoma	1
Anaplastic astrocytoma	1
Testicular cancer	1
Prostate cancer	1
Spinocellular carcinoma	1
Chronic lymphoblastic leukemia	1
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infections without the presence of identifiable underlying immunosuppressed status. Few cases were reported within the same family. The male to female ratio was 1.8:1.

ICL patients are susceptible for various opportunistic infections, including AIDS-defining illnesses. The majority of patients (87.6%) had at least one infection. Cryptococcal infections were the most prevalent infections in ICL patients (26.6%), followed by mycobacterial infections (17%), candidal infections (16.2%), and VZV infections (13.1%).

Malignancies were reported in 18.1% of the patients. Lymphoma with its subtypes, in general, was the most common reported malignancy in ICL patients. Autoimmune diseases were reported in 14.2% patients. Sjogren's disease was the most common reported autoimmune diseases in ICL patients. Kertava *et al.* retrospectively studied 115 patients with primary Sjogren's syndrome. Six patients met the criteria of ICL. One patient developed lymphoma in 3 years. They suggested that ICL patients should be screened for primary Sjogren's syndrome.^[33]

PATHOGENESIS

ICL is still considered a disorder of unclear etiology. Observational studies suggest factors related to CD4+ lymphocyte function, various immune defects, and genetic

elements. An investigation lead by the Centers for Disease Control (CDC) in early 1990's of 47 cases of ICL and their close contacts, sexual partners, children, blood donors, and recipients of the patients' blood did not demonstrate evidence of transmissibility.^[1] An extensive search for a viral etiology, utilizing serologic, culture, and PCR testing, was negative.^[105] However, Garry *et al.* demonstrated a cytopathic effect (CPE) of an ICL patient's peripheral blood mononuclear cells (PBMCs) co-cultured with a lymphoblastoid cell line, and identified A-type retroviral particles.^[55] In this same study, sera from 8 of 13 ICL patients reacted by Western immunoblotting with these retroviral particles, while control sera remained negative. However, those results were not duplicated in following studies.

Two factors related to CD4+ lymphocyte function play a role in developing ICL. First, increased activation of CD4, which may result from stimulation by an unidentified pathogen, resulting in a persistent decrease in the number of CD4+ lymphocytes.^[2] Lee *et al.* found increased levels of serum lipopolysaccharide (LPS) and markers of CD4+ lymphocyte activation in patients with ICL. Therefore, they hypothesized that abnormally increased microbial translocation through the intestinal wall may be an underlying etiology.^[146] Second, apoptosis of CD4+ lymphocyte may be associated with enhanced expression of Fas and Fas ligand. Roger *et al.* demonstrated that a patient with ICL and disseminated *Mycobacterium xenopi* infection had over expression of Fas/CD95c and spontaneous and Fas-induced apoptosis.^[119] However, patients with stable, physiologic, CD4 cell lymphopenia without opportunistic infections did not demonstrate accelerated apoptosis, suggesting that infection may be a necessary initial stimulus for this phenomenon.

Various other immune defects have been described in some ICL patients as well. Low CD8+ T cells counts were noticed in some patients. Patients with CD8 counts <180 cells/mm³ in a study of 39 patients were found to have a higher risk of serious opportunistic infections and death.^[5] This subgroup of patients may represent a more severe variant of ICL. The complete absence of specific CD8+ cells (CD8+ 28+) has been reported in a small number of patients with ICL.^[147] Defective expression of CXCR4, which binds the chemokine stromal cell-derived factor 1, on the surface of CD4+ cells, was noticed in six patients with ICL.^[148] The interaction of the receptor/ligand pair is critical for multiple aspects of normal T cell differentiation and trafficking. The alpha/beta and gamma/delta T cell repertoires of ICL patients are highly restricted, which may suggest a problem in maturation or differentiation during T cell development.^[68] Biochemical defects of the T cell receptor transduction pathway have been

noticed, possibly due to an abnormality of tyrosine kinase activity of p56 (Lck).^[13] Defects in this kinase appear to affect CD4 cell function and maintenance of adequate counts of cells. ICL has been associated with increases in immature or transitional B cells and increased serum levels of IL-7.^[149] Low B cell numbers or even a complete absence of B cells has been noticed in some patients.^[2,147] Isgrò *et al.* suggest that ICL may be due to decreased bone marrow clonogenic capability, or the inability of bone marrow stem cells to mature successfully.^[56]

Genetic factors might be involved in the pathogenesis of ICL as well. Zonios *et al.* found higher proportions of HLA-DR+ CD4 cells in ICL patients compared to controls, which suggests that there could be a genetic predisposition to ICL, or that ICL is more common in certain populations.^[2] Hypomorphic mutations in the recombination activating gene 1 (RAG1) were identified in a patient with Varicella infection and recurrent pneumonias.^[58]

Non-ICL causes of CD4 lymphocytopenia

Various infections, malignancies, and medications can depress the CD4 counts. HIV is the most important cause of CD4 lymphocytopenia. Transient CD4 lymphocytopenia is common and has been estimated to occur in healthy HIV-negative individuals within a 95% confidence interval from 0.4-4.1% at any given time.^[150] Infections, malignancies, medications and autoimmune diseases can lead to transient CD4 lymphocytopenia. Opportunistic bacterial,^[151] viral, parasitic, and fungal diseases may depress CD4 cell counts, but usually without inversion of the CD4:CD8 ratio.^[152,153]

CD4 lymphocytopenia was found in 9.6% of HIV-negative hospitalized tuberculosis patients and in 4.2% of ambulatory tuberculosis patients.^[154] Another study showed that CD4 lymphocyte counts below 300 cells/ml were found in 14.4% of HIV-seronegative inpatients with tuberculosis.^[96] Lymphocytopenia was noticed to be associated with a more severe course of mycobacterial infections.^[96,155] Cytomegalovirus infection can depress CD4 cells and produce a marked increase in CD8 counts, and therefore, an inverted CD4:CD8 ratio. Resolution of cytomegalovirus disease was associated with resolution of those altered counts.^[153] Human T-cell lymphotropic virus type II (HTLV-II) is capable of altering CD4 counts for prolonged periods of time in a portion of intravenous drug users and homosexual men.^[156]

Large cell lymphoma, mucosa-associated lymphatic tissue (MALT) lymphoma, and Burkitt's lymphoma are associated with lymphocytopenia with usually a normal CD4:CD8

ratio.^[157] A study evaluated 214 patients with primary Sjögren's syndrome and detected CD4 lymphocytopenia below 300 cells/ml in eight patients (3.7%).^[158] In SLE patients, decreased numbers of CD4 T cells and a low CD4:CD8 ratio were associated with severe renal disease or thrombocytopenia.^[159,160] Immunosuppressants such as steroids, cyclophosphamide, azathioprine, and methotrexate might cause CD4 lymphocytopenia. In a study that evaluated CD4 cell counts in patients receiving immunosuppressants, cyclophosphamide produced a more severe depression in lymphocytes and CD4 cells than azathioprine and methotrexate.^[161]

Prophylaxis and treatment

Due to the rarity of this condition, no specific guidelines exist for prophylaxis, monitoring, and treatment. Therefore, the management is based on the experience with HIV treatment. Prophylaxis against opportunistic infections is advised using the protocols advocated for HIV-1 infected patients with advanced disease. Monitoring every four months with CD4 counts might be sufficient for stable patients without apparent infections. Once those patients develop signs of infection, they need close attention.

In the prospective study by Zonios *et al.*, the CD4 T-cell counts in their patients remained less than 300/mm³ for several years with absence of progression of lymphocytopenia over time. One-fifth of their patients resolved their lymphocytopenia within 3 years of diagnosis. Therefore, they suggested that it is reasonable to consider following ICL patients more closely during the first 3 years because of the risk of serious infections and the possibility if normalization of CD4 T-cell counts, allowing discontinuation of any prophylaxis if initially given.^[2]

Zonios *et al.* in another study followed 11 patients with cryptococcosis and idiopathic CD4 lymphocytopenia (ICL) referred to their institution, as well as 42 similar cases reported in the literature. Different treatment regimens were used in cryptococcal infections. Therefore, one cannot compare the effectiveness of these regimens. The relapse rate of cryptococcal infections in ICL patients is low compared to HIV patients. ICL patients with cryptococcal infections have a favorable outcome in general.^[22]

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+ lymphopenia. IL-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.^[30,50,72,93,101]

Limitations

Case reports varied in quality and completeness. Although all cases were published as ICL, one can still question the diagnosis, especially in cases with conditions which are known to depress CD4 counts, like mycobacterial infections and malignancies. One example is a case that was diagnosed with aplastic anemia four months after the diagnosis of ICL. That patient underwent a bone marrow (BM) biopsy on presentation and two months after presentation. Both biopsies were negative for malignancy or aplasia. On a third biopsy four months after presentation, aplastic anemia criteria were met. One could very easily argue that aplastic anemia probably existed at the time of presentation since the diagnosis of aplastic anemia was done just four months after and explains the depressed CD4 counts.^[131]

Relationship between the level of CD4 and CD8 and the opportunistic infections could not be made because many patients had several opportunistic infections, but the counts were recorded around one opportunistic infection only.

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