Idiopathic CD4 Lymphopenia: Severe CD4 Lymphopenia in the Absence of Human Immunodeficiency Virus Infection

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Severe lymphopenia, mainly severe CD4 cell lymphopenia, is one of the hallmarks of human immunodeficiency virus (HIV)-1 (as well as HIV-2) infection [1]. The low CD4 cell counts in those patients is the main cause for serious specific opportunistic infections and malignancies [2]. Idiopathic CD4 lymphopenia (ICL) was described and defined in 1992 by the American Centers for Disease Control and prevention (CDC) as a persistent CD4 lymphopenia < 300 cells/μl without evidence of HIV infection or any other cause of the depressed CD4 cell counts [3]. It is a rare disease: of the 230,129 suspected cases that the CDC found and defined, only 47 patients had ICL [4]. In this review we present the definition, pathogenesis, diagnostic criteria, epidemiology, clinical course and treatment options for ICL.

> Idiopathic CD4 lymphopenia is a rare disease characterized by low (< 300 cells/μl) CD4 cell counts in the absence of HIV and other secondary causes

The diagnosis of ICL requires the presence of the following criteria:

- Low CD4 cell counts (in peripheral blood) < 300 cells/μl or < 20% of the total lymphocyte counts in two separate tests (at least 6 weeks apart)
- No evidence of HIV-1 or HIV-2 infections
- The absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 [3].

Although most ICL cases were reported to have low a CD4/CD8 ratio [5], the CDC definition for ICL diagnosis does not exclude patients with panlymphopenia (low CD4 and CD8) and normal CD4/CD8 ratio [6].

The pathogenesis for ICL has not yet been defined. Decreased CD4 cell production and differentiation, and increased destruction with tissue sequestration (such as spleen and lymph nodes) are most probably involved in the pathogenesis of ICL [7]. Disturbed thymic T cell maturation was observed in some ICL patients [8]. In other patients, over-expression of Fas or Fas ligand (enhanced apoptosis) was reported [9]. Several studies reported the expansion of T cells [10] with defective production of interferon (IFN) α and γ [11] representing disturbed T cell differentiation. High interleukin (IL)-7 levels caused by decreased IL-7 receptor levels on CD4 cells may also contribute to ICL [12]. Recently, mutations in several genes (*RAG1*, *NAGT1*, and *UNC119*) were described in a few patients with low CD4 cell counts [reviewed in 7]. However, according to the CDC diagnostic criteria, the defined genetic etiology excluded the diagnosis of ICL.

In contrast to HIV infection, in most patients with ICL there is no decrease in CD8 cell counts and the number of B cells is within the normal limits without the hypergammaglobulinemia observed in many HIV-infected patients [6]. The CD4 cell levels in ICL patients are stable (without significant decline during follow-up) over a long period of time [13] in contrast to HIV-infected patients in whom without treatment CD4 decline is mandatory.

ICL is a rare disease; fewer than 300 cases have been reported [14] but the true prevalence of the disease is unknown. The mean age of the patients at the time of ICL diagnosis is 41 ± 19 years (range 1–85) with a slightly higher male predominance (60%). Only a few familial cases have been reported [15,16].

There is no indication that ICL is caused by a transmissible infectious agent, and ICL was not reported to be associated with any of the risk factors for HIV, e.g., males who have sex with males, intravenous drug users, or sex workers [14].

In order to make the diagnosis of ICL in patients with low CD4 cell counts one must exclude all known or possible causes of CD4 lymphopenia (in addition to HIV). In those cases of secondary CD4 lymphopenia, the CD4 cell count

Table 1. Suggested primary and secondary prevention for opportunistic infections in ICL patients

Opportunistic infection	Criteria for initiating prophylaxis		Criteria for discontinuing prophylaxis	
	Primary	Secondary	Primary	Secondary
Cryptococcosis	Not recommended	Prior cryptoccocal meningitis	Not applicable	CD4 > 100 cells/µl for at least 3 months
Pneumocystis pneumoniae	CD4 count < 200 cells/ µl	Prior *P. pneumoniae*	CD4 count increased to > 200 cells/µl for > 3 months	CD4 count > 200 cells/µl for > 3 months
Toxoplasmosis	CD4 count ‹ 100–200 cells/µl	Prior toxoplasmosis	CD4 count increased to > 200 cells/µl for >3 months	CD4 count > 200 cells/µl for › 6 months
Mycobacterium avium complex	CD4 count ‹ 50 cells/µl	Prior *M. avium* disease	CD4 count > 100 cells/µl for ≥ 3 months	Completed ≥ 12 months of therapy and CD4 count › 100 cells/µl for › 6 months

* The above prevention regimens are based on the Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. http://aidsinfo.nih.gov/guidelines, 04/11/2016 [23]

may be severely low (< 300 cells/µl) but it is usually transient (improved following treatment of the primary pathogenic cause, or following the withdrawal of the causative immunosuppressive drug) [17].

The main causes of secondary lymphopenia include mycobacterial infections (mainly tuberculosis), viral infections (HIV, cytomegalovirus, Epstein-Barr virus, hepatitis B and HTLV1), malignancy (non-Hodgkin's lymphoma, myelodysplastic syndrome), autoimmune disorders (Sjogren syndrome, systemic lupus erythematosus), and drugs such as corticosteroids, chemotherapy and cytotoxic agents [reviewed in 13].

The clinical spectrum of ICL varies. ICL patients may be asymptomatic for many years. In those cases the CD4 lymphopenia is discovered accidentally. However, most of the patients have opportunistic infections similar to those observed in HIV patients with low CD4 cell counts [18]. Indeed, most ICL patients are diagnosed following an opportunistic infection or after recurrent opportunistic infections. The main opportunistic infections reported in ICL patients include *Mycobacterium tuberculosis*, *Mycobacterium avium* intracellular, *Salmonella typhimurium*, cytomegalovirus, John Cunningham virus (JC virus), human papillomavirus, varicella zoster virus, herpes simplex virus, human herpes virus-8, *Aspergillus* spp, *Candida albicans*, *Cryptococcus neoformans*, *Pneumocystis jirovecii* and toxoplasmosis [reviewed in 19]. Cryptococcosis is the most common opportunistic infection reported in ICL patients followed by *M. tuberculosis* and herpes zoster infections [6]. Because of the high risk for herpes virus-8 and human papillomavirus infections in ICL patients, disseminated Kaposi sarcoma and human papillomavirus-related malignancies should be looked for in ICL patients [18-20]. The main differential diagnosis in a patient with suspected ICL is HIV infection, but patients with ICL have negative HIV serology and HIV polymerase chain reaction [21].

The management of ICL patients is aimed at treating and/or preventing opportunistic infections and increasing the number of CD4 lymphocytes. Opportunistic infection should be treated according to the specific infection. There are no accepted guidelines for primary and secondary infection prevention in ICL patients. We, as well as others [22], suggest following the current primary and secondary prevention recommendations used in HIV patients which is based on the number of CD4 cell counts [23] [Table 1]. There is no way of predicting the clinical course of a particular ICL patient (based on his or her laboratory results, e.g., the number of CD4 cells) [6]. However, a patient with recurrent opportunistic infections should be treated aggressively (including primary and secondary prophylaxis).

The efficacy of vaccination in ICL patients is unknown. In HIV patients CD4 cell counts > 400 cells/µl are associated with good (normal) response to vaccination, whereas in patients with lower CD4 cell counts a poor efficacy was reported [24]. Live vaccines are contraindicated and should be avoided in ICL patients. All other types of vaccines (dead, recombinant) may be given but their efficacy and protective effects are not known and are unpredictable.

A few case reports suggested the efficacy of IL-2 therapy in patients with ICL. IL-2 infusion in ICL patients was shown to increase CD4 cell counts [25] and prevent the reoccurrence of cryptoccocal meningitis [26] and relapsing herpes zoster virus infection in patients with ICL [27]. Treatment with IFNγ was also shown to increase CD4 cell counts in four ICL patients, leading to sustained clinical amelioration of cryptoccocal meningitis and of non-tuberculous mycobacterial infection [28]. In animal models (*Rhesus masques*), recombinant IL-7 was shown to induce CD4 cell proliferation [29]. Currently there are no human studies with IL-7 in ICL patients. Allogeneic bone marrow transplantation was successfully performed in one ICL patient [30]. Taken together, cytokine treatments for ICL may be beneficial, but since the clinical experience with such treatments is limited, its real efficacy remains undefined.

To conclude, ICL is a rare immunological disorder characterized by persistent low levels of CD4 cell counts (< 300 cells/µl).

The initial presentation is usually an opportunistic infection

Treatment with different cytokines to raise CD4 counts looks promising but data are limited

The etiology of ICL is unknown. Most patients are diagnosed following an opportunistic infection. It is mandatory that HIV diagnosis be excluded in all ICL patients. The guidelines for primary and secondary infectious prevention of ICL are not yet established but we recommend following the prevention policy used in HIV patients. Novel biological treatments aimed at increasing CD4 cell counts are of great interest but their real efficacy is still undetermined.

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"It's good to have money and the things that money can buy, but it's good, too, to check up once in a while and make sure that you haven't lost the things that money can't buy"

George H. Lorimer (1867-1937), American journalist and author, best known as the editor of *The Saturday Evening Post*

"The noblest of all dogs is the hot-dog; it feeds the hand that bites it"

Laurence J. Peter (1919-1990), Canadian educator and "hierarchiologist" best known for the formulation of the Peter Principle, whereby "In a hierarchy every employee tends to rise to his level of incompetence." The Peter Principle became one of the most profound principles of management from the University of Southern California