Idiopathic CD4 lymphocytopenia

Ulrich A. Walker and Klaus Warnatz

Purpose of review

A severe decrease of CD4 T cells predisposes humans to opportunistic infections. In adults, HIV is certainly the most common cause of CD4 lymphocytopenia, but other causes, such as infections, autoimmune diseases, immunosuppressive therapy, lymphoma and idiopathic forms need to be considered. This review summarizes the current knowledge of the poorly understood syndrome of idiopathic CD4 lymphocytopenia.

Recent findings

Little research has tried to systematically dissect this probably heterogeneic syndrome after its initial description in 1992. Numerous cases presenting with opportunistic infections have been reported. Disturbed differentiation of stem cell precursors may contribute to CD4 lymphocytopenia. Because infections and lymphoma may also cause CD4 lymphocytopenia, the distinction between cause and effect may evolve only during follow-up.

Summary

The manifestation of opportunistic infections calls for the evaluation of the immune system for CD4 lymphocytopenia. The differential diagnosis of this condition in adults comprises primarily HIV infection and less often other diseases or drugs. Idiopathic CD4 lymphocytopenia is very rare. The clinical significance of low CD4 cell counts in HIV negative patients still awaits its systematic analysis. Prophylaxis of opportunistic infections is oriented at the recommendations of HIV-infected individuals and causal treatment remains experimental.

Keywords

CD4 count, immunodeficiency, lymphocytopenia, opportunistic infection, T4 cells

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Division of Rheumatology and Clinical Immunology, Freiburg University Hospital, Freiburg, Germany

Correspondence to Klaus Warnatz, MD, Division of Rheumatology and Clinical Immunology, Freiburg University Hospital, Hugstetterstr. 55, D-79106 Freiburg, Germany
Tel: +49 761 2703401; fax: +49 761 2703306; e-mail: klaus.warnatz@uniklinik-freiburg.de

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Abbreviations

CDC Centers for Disease Control and Prevention
ICL idiopathic CD4 lymphocytopenia

1040-8711

Introduction

In 1992, idiopathic CD4 lymphocytopenia (ICL) was defined by the US Centers for Disease Control and Prevention (CDC) as including patients with depressed numbers of circulating CD4 T lymphocytes (< 300 cells/μl or $< 20\%$ of total T cells) on a minimum of two separate time points at least 6 weeks apart, with no laboratory evidence of infection with human HIV-1 or HIV-2, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells [1]. The provisional case definition by the CDC therefore also permits the inclusion of patients with panlymphocytopenia and normal CD4 : CD8 ratio, although most of the published cases had a severely inverted CD4 : CD8 ratio.

The same phenomenon is referred to as severe unexplained HIV-seronegative immune suppression by the World Health Organization, with the additional requirement that the patient has a disease indicative of a cellular immune deficiency [2].

Epidemiology

Unlike transient CD4 lymphocytopenia, which 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 [3], ICL of the adult is very rare. No case was identified in one study that screened 2028 blood donors [4], and 1.4% of heterosexuals in another cohort of 676 donors [5]. In the original survey of 47 ICL patients [6], there was no detectable bias in sex (29 males : 18 females) or age at diagnosis (43 ± 14 years; range 17–78). Only few familial cases were presented [7,8] and there is no indication that ICL is transmitted sexually.

Pathogenesis

The few investigations of the pathogenesis of ICL suggest a diminished generation of T cell precursors. Bone marrow analysis of five ICL patients revealed a significant decrease of early CD34+CD38-DR+ hematopoietic stem cells (1.2 ± 0.1 versus 5.6 ± 1.2 in healthy controls) and a decreased clonogenic capacity of bone marrow progenitors [9•]. The same group has described similar results for common variable immunodeficiency patients with low CD4 cell counts [10] and implicated a disturbed cytokine environment such as increased tumor necrosis factor (TNF)-α and decreased IL-2 levels as a reason for the impeded differentiation of progenitor cells. Serum IL-7, a master regulator of T cell homeostasis was

increased and hence probably reflects a compensatory mechanism [9•]. Decreased numbers of peripheral $CD45RA^+$ positive naïve T cells and a relative expansion of $CD45RO^+$ T cells reflect the low thymic output in patients with thymic hypoplasia [11], or the disturbed differentiation of thymocytes in patients with Omenn syndrome [12]. In addition accelerated apoptosis especially of $CD45RO^+$ memory type CD4 T lymphocytes (seven of eight patients) [13,14], decreased proliferative capacity partly due to disturbed T cell receptor signaling (two of two patients) [15] and a deficient IL-2 production [16] were documented in a variety of patients. All these findings are thought to contribute to the restricted oligoclonal T cell receptor repertoire [17] that was identified in most of the patients analyzed.

Immunologic phenotype

In most patients, immunologic phenotyping of ICL reveals a concomitant, less pronounced decrease of CD8 cells, a slightly decreased CD4:CD8 ratio and normal B cell numbers. Unlike in HIV infection the progression of the decline of CD4 cell counts is slow or even absent over a long period. Among the CD4 cells, naïve $CD45RA^+$ T cells are more severely diminished than the $CD45RO^+$ memory population. Unlike HIV-infected patients, hypergammaglobulinemia is rarely present [18]. Several reports describe an expansion of $\gamma\delta$ T cells in these patients [19,20], which may be the result of a disturbed T cell differentiation or of concomitant infections [19]. The reported increase in Fas^+ T cells is most likely a consequence of the relative expansion of memory T cells, which express Fas, and therefore the reports of increased apoptosis [13,14] need to keep the altered T cell homeostasis of ICL in mind.

Secondary forms of CD4 lymphocytopenia and differential diagnosis

The differential diagnosis of secondary CD4 lymphocytopenia in adults is reviewed in Table 1 [21–30,31•,32–36].

Table 1 Differential diagnosis of CD4 lymphocytopenia in adults

Type	Diagnosis
Infections	
Mycobacteria	*Mycobaterium tuberculosis* [21]
	Atypical mycobacteria
Viral	Cytomegalovirus
	Ebstein–Barr virus
	Hepatitis B virus
	HIV (www.hivnet.org)
	Human T cell lymphotropic virus 1 and 2 [22]
	Influenza
	Severe acute respiratory syndrome [23]
Malignancy	Non-Hodgkins, lymphoma [24]
	Mycosis fungoides [25]
	Aplastic anemia [26]
	Myelodysplastic syndrome [27]
Autoimmune diseases	Sjögren's syndrome [28]
	Systemic lupus erythematosus [29]
	(Rheumatoid arthritis [30])
Drugs	Corticosteroids [31•]
	Chemotherapy and cytotoxic immunosuppressants [31•] cyclophosphamide, azathioprine, methotrexate
	Others (cephalosporin, IFN-α)
Primary immunodeficiency syndromes with possible adult onset	Common variable immunodeficiency [32] subtype
	Adult onset adenosine deaminase deficiency [33]
	Bare lymphocyte syndrome type I (very rare mutation of TAP protein)
Miscellaneous conditions	Erythroderma [34] and severe burns
	Radiation therapy [35]
	Malnutrition [36]

Infections

The most important differential diagnosis of low CD4 lymphocytopenia is HIV infection. Common pathogenic and opportunistic bacterial [37], viral (hepatitis B, Ebstein–Barr virus, cytomegalovirus), parasitic, and fungal diseases may depress CD4 cell counts, but often without inversion of the CD4:CD8 ratio [38,39]. The changes associated with these infections are mostly transient and therefore probably 'physiologic' responses to an alteration of the cytokine and inflammatory environment. Even immunizations may alter absolute numbers of T-cell subsets in up to 25% of cases [40].

CD4 lymphocytopenia has been associated with extrapulmonary tuberculosis. In a retrospective study in Côte d'Ivoire T lymphocyte counts below 300 cells/μl were found in 9.6% of 115 HIV-negative hospitalized tuberculosis patients, in 4.2% of 312 ambulatory tuberculosis patients, compared to 0.4% of 263 healthy women after delivery [41]. Similarly, a prospective study in Senegal observed CD4 T lymphocyte counts below 300 cells/μl in 14.4% of 430 HIV-seronegative inpatients with tuberculosis [42]. Lymphocytopenia was associated with a more severe course of mycobacterial infections [42,43]. Several patients with disseminated mycobaterial infection demonstrated significant improvement of CD4 T-lymphocyte counts after 4–8 weeks of antituberculous therapy, suggesting that the infection is the cause rather than the consequence of CD4 lymphocytopenia [21,44].

Acute cytomegalovirus infection produces a depression of CD4 cells and a marked increase in CD8 counts, and thus an inverted CD4:CD8 ratio. These abnormalities return to baseline after resolution of cytomegalovirus disease, with no difference between cytomegalovirus-seropositive and seronegative persons [38]. Human T-cell lymphotropic virus type II (HTLV-II) has been identified in a substantial portion of intravenous drug

users and homosexual men and is capable of altering CD4 counts for prolonged periods of time [22].

Malignancy

Several hematological malignancies may cause CD4 lymphocytopenia. Non-Hodgkin's lymphoma [large cell lymphoma, mucosa associated lymphatic tissue (MALT) lymphoma, and Burkitt's lymphoma] as well as mycosis fungoides [25] were described in association with lymphocytopenia and usually with a normal CD4 : CD8 ratio [45]. A patient with myelodysplastic syndrome (refractory anemia) developed CD4 lymphocytopenia, along with life-threatening listeriosis, tuberculosis, and progressive multifocal leukencephalopathy [27].

Autoimmune diseases

A study of 214 patients with primary Sjögren's syndrome detected CD4 lymphocytopenia below 300 cells/μl in eight patients (3.7%) [46]. Anti-CD4 antibodies were discovered in 13% of the population, but there was no correlation with CD4 counts. The same group, however, described a strong association of CD4 lymphocytopenia with the presence of anti-Sjögren's syndrome antigen A-(SSA)autoantibodies (16 versus 0%) [47]. Serious opportunistic infections are rare in patients with Sjögren's syndrome and CD4 lymphocytopenia [48].

In contrast to patients with Sjögren's syndrome, CD4 lymphocytopenia was associated with the presence of a variety of anti-lymphocytic antibodies in individuals with systemic lupus erythematosus (SLE) [29]. In another analysis of SLE patients, decreased numbers of CD4 T cells and a low CD4 : CD8 ratio were associated with severe renal disease or thrombocytopenia, but not other manifestations [49,50]. The risk of opportunistic infections in autoimmune patients with CD4 lymphocytopenia is not known, but there were cases with severe opportunistic infections such as cryptococcal meningitis [51].

Medication

A cross-sectional study of 97 patients with autoimmune disease analyzed the effect of immunosuppressive therapy on lymphocyte and CD4 T cell counts and the rate of infections [31•]. In all patients on immunosuppressants a correlation between corticosteroid dose and lymphocyte as well as CD4 cell counts was observed. Cyclophosphamide produced a more severe depression in lymphocytes and CD4 cells (all below 250 cells/μl) than azathioprine and methotrexate. CD4 T cell counts below 250 cells/μl represented the highest risk factor for subsequent hospitalization due to infection. Most of the infections were bacterial and only a few opportunistic. The authors suggest screening patients on severe immunosuppressive treatment for an increased risk of infection with CD4 monitoring. The cross-sectional data, however, do not truly allow separating disease from treatment related risks.

Other factors associated with altered CD4 cell counts

Other factors that influence the peripheral CD4 cell count include age, sex, circadian rhythm, and smoking, but only very rarely these factors were associated with CD4 counts in the range of ICL [38]. Patients admitted to an intensive care unit had CD4 counts below 200 cells/μl in 17% of cases, usually reflecting panlymphocytopenia (normal CD4 : CD8 ratio) [52]. This panlymphocytopenia was associated with a 2.5-fold risk of death. Down's syndrome [53] also predisposes for panlymphocytopenia partially recovering with increasing age.

Clinical features of idiopathic CD4 lymphocytopenia

The clinical spectrum of ICL ranges from an asymptomatic laboratory abnormality to life-threatening complications that imitate the clinical course of HIV-infected patients. The original study by the CDC ICL task force [6] described 19 patients (40%) with AIDS-defining illnesses, 25 (53%) with non-AIDS-defining conditions, and three asymptomatic patients (6%).

Infections

CD4 lymphocytopenia typically became apparent through the manifestation of opportunistic infections (see Table 2) [54–89].

Cryptococcosis is the most commonly described infection in the literature, followed by mycobacteriosis and multisegmental herpes zoster. This order is, however, most

Table 2 Opportunistic and atypical infections in patients with idiopathic CD4 lymphocytopenia

Class	Agent
Bacterial	*Fusobacterium nucleatum* [54]
	Mycobaterium tuberculosis [55]
	M. avium intracellulare [56,57]
	M. chelonae [58]
	M. kansasii [57]
	M. mucogenicum [59]
	Nocardia spp. [60]
	Salmonella typhimurium [61]
Viral	Cytomegalovirus [57,60,62–64]
	Herpes simplex virus
	Human papilloma virus [65–68]
	Human herpes virus-8 [69]
	JC virus [70,71]
	Molluscum contagiosum virus [72]
	Varicella zoster virus [67,73,74]
Fungal	*Aspergillus* spp. [57,75]
	Candida albicans [67]
	Cryptococcus neoformans [76–84]
	Encephalitozoon cuniculi [85]
	Exophiala jeanselmei [58]
	Histoplasma capsulatum [84,86]
	Pneumocystis jirovecii [84,87,88]
Protozoan	Toxoplasmosis [89]

likely subject to publication bias and does not represent true incidences.

Disseminated Kaposi's sarcoma, an infection with human herpes virus-8, developed in five patients with severe reduction of CD4 counts [69,90–93] partly in combination with steroid treatment (two patients) or hypogammaglobulinemia (two patients).

Malignancy

The diagnosis of a B-cell non-Hodgkin's lymphoma several years after the onset of CD4-lymphocytopenia raises the possibility, that the malignancy was a consequence rather than the cause of immunodeficiency in some patients [94].

This was corroborated by other diffuse large B-cell non-Hodgkin's lymphoma and one case of Burkitt lymphoma in which the lymphocytopenia also preceded the malignancy for years and in which the CD4 lymphocytopenia persisted after complete remission of the lymphoma [95–97].

Given the increased risk of severe human papilloma virus infections in patients with ICL, the association of certain papilloma virus types with cervical cancer and the increased frequency of this cervical cancer in HIV-infected females, it is likely that women with ICL carry an increased risk of developing cervical neoplasias (although this has not been investigated).

Treatment

The treatment of CD4 lymphocytopenia consists of the therapy of underlying conditions, treatment and prophylaxis of secondary complications, especially of opportunistic infections, and the still experimental approaches to enhance CD4 T cell counts.

At this time one cannot predict the clinical course on the basis of laboratory markers. The occurrence of multiple opportunistic infections and relapses in individual patients suggests that an aggressive approach to diagnosis, treatment, and prophylaxis is needed.

In CD4 lymphocytopenia in association with mycobacterial infections, several reports describe the improvement of CD4 T cell counts with antimycobacterial treatment [21]. In autoimmune disease, lymphocytopenia may recuperate with treatment of the underlying disease, but often persists despite remission. In the case of severe lymphocytopenia secondary to immunosuppressive drugs, the regimen should be deescalated, if possible.

Symptomatic treatment and prophylaxis

HIV-patients are at risk for opportunistic infections, when CD4 counts fall below 200 cells/μl (www.hiv.medicine.com). Clear guidelines for patients with both idiopathic and non HIV-related secondary CD4 lymphocytopenia are not available, thus the current recommendations are oriented mainly on the experience with HIV-infected patients. On the other hand the clinical course of an individual patient needs to be taken into account. Prophylaxis against pneumocystis is recommended when CD4 T cell counts fall below 200 cells/μl [84]. Cryptococcosis as well as relapsing multisegmental herpes infection may require secondary prophylaxis for lifetime. Women should be screened for cervical neoplasia every 6 months. For hepatitis B and C, prophylaxis and treatment should also be oriented at the recommendations for patients with HIV infection.

There are no systematic data on the efficacy of vaccination in HIV negative patients with low CD4 T cell counts. While life vaccines are contraindicated, dead vaccines may be given, albeit without a predictable protective effect. HIV-infected patients with CD4 cells below 100 cells/μl produced usually no detectable response to the vaccination [98,99], while a diminished and less durable response was detected in HIV patients with CD4 cell counts below 300 cells/μl for several vaccines (hepatitis B, tetanus, influenza, pneumococcal polysaccharides) [99–101].

Strategies to increase CD4 lymphocytes

Few reports [16,64] suggested IL-2 therapy for ICL as an option to increase CD4 counts and thereby also decrease the susceptibility to infection. Several trials of IL-2 in HIV infection [102,103••,104] and other immunodeficiencies (common variable immunodeficiency [105], severe combined immunodeficiency [106]) demonstrated an early increase of CD45RO memory, followed by a rise in CD45RA CD4 T cells [107]. The ultimate benefit of increased CD4 counts with regard to the incidence of infections, however, remains uncertain. The first ICL patient with severe CD4 lymphocytopenia (< 50 cells/μl) receiving weekly 50 000 IU/m^2 of pegylated IL-2 [16] was treated for persistent infection with atypical mycobacteria. CD4 cells including CD45RA naïve CD4 cell counts improved slowly and the patient had no relapse of mycobacteria despite discontinuation of antimycobacterial therapy after 5.5 years. A second 65-year-old patient had relapsing generalized herpes zoster infections despite antiviral prophylaxis [74] and was treated with five times 3 000 000 IU every other week. Within the first 6 months of therapy, CD4 counts increased from 24 to 100 cells/μl. Antiviral therapy was discontinued without relapse. After about 1 year of intermittent IL-2 therapy the patient was diagnosed with gastric anaplastic large cell MALT lymphoma and died within 1 month. Previous tumor screening including gastroscopy had been negative (unpublished data, [74]). The relationship between the evolving lymphoma and the IL-2 therapy remains unclear but suggests careful exclusion of preexisting and monitor-

ing of evolving lymphoma in patients with disturbed T cell differentiation like ICL patients. While further experience with IL-2 therapy in ICL patients is needed, to support the hope that this cytokine may be a therapeutic option, other cytokines like IL-7 are being tested [108•].

Two cases were recently described in which the assessment of cytokines released revealed a defective production of the proinflammatory cytokines IFN-γ and TNF-α in response to injection. One patient with progressive cryptococcal meningitis despite receipt of antifungal treatment was administered recombinant IFN-γ. IFN-γ then resulted in a sustained clinical recovery from *Cryptococcus* [78].

Allogeneic bone marrow transplantation (BMT) was performed in one ICL patient for a concomitant aplastic anemia [26]. Subsequently immune function was completely restored and the authors suggested BMT as a potential cure for ICL. As often in rare diseases with an obscure prognosis, however, it is difficult to identify the patients and timing that will benefit most.

Conclusion

In the future, idiopathic and secondary forms of HIV-negative CD4 lymphocytopenia will need a better immunologic characterization to improve the diagnostic definition, to guide prognosis and to individualize treatment in this heterogeneous syndrome.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 441).

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