

Idiopathic CD4 lymphocytopenia

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ABSTRACT

Background: Idiopathic CD4 lymphocytopenia (ICL) is a rare disorder of unknown etiology. Diagnostic criteria include a persistent CD4 T-cell lymphopenia with no underlying primary or secondary immune deficiencies and a CD4 T-cell count of <300 cells/mL or <20% total lymphocyte on multiple occasions.

Objective: To increase awareness of ICL and to provide a review of the clinical characteristics, diagnosis, and management of this disease process. Presently, many of these patients receive prophylactic treatment similar to other T-cell deficient conditions, most notably patients with human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome; however, the same indications may not necessarily apply to this patient population because the T cells are not affected by a virus as in HIV.

Methods: A literature search of salient articles that describe case reports and case series of ICL and their management were analyzed.

Results: A case of ICL with a literature review is presented with emphasis on clinical pearls and pitfalls. The patients with ICL are usually identified with a CD4 count of <200 cells/mL when complications develop. Opportunistic infections are the most common initial manifestations. Current therapies used to increase CD4 levels include interleukin 2, interferon gamma, interleukin 7, and allogeneic hematopoietic stem cell transplantation, with variable results.

Conclusion: ICL is a diagnosis of exclusion when there is no identifiable underlying cause for a low CD4 count. Although the nature of the T-cell problem is not the same in ICL and HIV, in the absence of specific guidelines, patients receive the same prophylactic treatment as patients with HIV.

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Question:

A 52-year-old white woman, with a history of systemic lupus erythematosus, well controlled on hydroxychloroquine, presented with a 2-month history of progressive headaches associated with confusion, dizziness, nausea and/or vomiting, and right eye pain. No focal neurologic deficits were found on examination. Brain magnetic resonance imaging revealed linear leptomeningeal enhancement, suspicious for meningoencephalitis. *Cryptococcus neoformans* grew on cerebrospinal fluid culture. Antifungal therapy was initiated with amphotericin B and flucytosine.

A thorough immunologic workup revealed normal results except for an initial absolute CD4 count: 86 cells/mm³ (Normal: >500). Repeated studies revealed

an absolute CD4 of 37 cells/mm³ and CD8 count of 91 cells/mm³ (Normal: >200), and a CD4:CD8 ratio of 0.41. In the studies performed for causes of low CD4 count, results, including human immunodeficiency virus (HIV) testing with polymerase chain reaction, other infectious etiologies, sarcoidosis, autoimmune conditions, and malignancies, were all negative. A review of outside records revealed that the patient was diagnosed with systemic lupus erythematosus due to symptoms of joint pains and fatigue, with an antinuclear antibody titer of 1/160, but results for other antibodies were negative. The patient was started on hydroxychloroquine, with significant improvement of her symptoms. On this admission, her C3 and C4 levels were within normal ranges, and she did not have any signs or symptoms suggestive of systemic lupus erythematosus.

Trimethoprim (TMP) and sulfamethoxazole (SMX) daily was added for *Pneumocystis jirovecii* prophylaxis. Although adequately covered with antibiotics for toxoplasmosis, she did not require prophylaxis because she had negative results for *Toxoplasma gondii* immunoglobulin G value. Based on the patient's presentation, laboratory findings, and no identifiable

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cause for the low CD4 count, the diagnosis of idiopathic CD4 lymphocytopenia (ICL) was made. The patient was discharged on intravenous amphotericin daily, oral flucytosine, and TMP/SMX daily. The patient was adherent to her medication use and remained asymptomatic at all subsequent follow-up outpatient visits. Her CD4 count remained low, at <100 cells/mm³, but she did not develop any further opportunistic infections. Subsequently, the patient was continued on fluconazole and TMP/SMX. The patient continued to be followed up and remained free of opportunistic infections after 22 months.

Which of the following is true?

Possible Answers:

- A. There are guidelines for prophylactic treatment specific to patients with ICL.
- B. Patients with ICL often have multiple immune system abnormalities.
- C. *C. neoformans* is the most common infectious organism identified in patients with ICL.
- D. The pathogenesis of ICL is well defined.
- E. ICL is a disease of adulthood.

Idiopathic CD4 lymphocytopenia (ICL) is a rare disorder of unknown etiology. It was first defined by the U.S. Centers for Disease Control and Prevention in 1992, with the first suspected cases reported in the literature in 1989. The diagnostic criteria includes a persistently low absolute CD4 count of <300 cell/mL and/or $<20\%$ total lymphocytes on multiple occasions in the absence of primary or secondary causes of immunodeficiencies.¹ Zonios *et al.*² reported at least 2 ICL subtypes, dependent on the presence or absence of CD8 T-lymphocytes. Patients with ICL and CD8 T-lymphocytopenia were at a higher risk for infections and had a worse overall prognosis.² The U.S. Centers for Disease Control and Prevention definition permits the inclusion of cases with panlymphocytopenia and both normal and abnormal CD4:CD8 ratios.³

The current prevalence of ICL is unknown. There is no sex predilection. This disease was originally thought to be a disease of adulthood. However, several cases have been reported among the pediatric population as well. There are limited data on patients with asymptomatic ICL. The majority of patients present with opportunistic infections as part of their initial concern. However, patients may also present with malignancies or autoimmune diseases.^{4,5} A broad differential should be maintained when evaluating these patients.

CLINICAL CHARACTERISTICS

ICL has a heterogeneous presentation that is dependent on the degree of immunosuppression. In the lit-

erature, the reported incidence of patients who are asymptomatic ranges from 6 to 13%.^{1,5} Patients with mild immunosuppression may experience oral thrush or recurrent herpes zoster. Patients frequently present with opportunistic infections when their CD4 count is <200 cells/mL. Cryptococcal meningitis is the most common presentation. Other infections include candidal; *Pneumocystis pneumonia*; mycobacterial; and viral, including human papilloma virus, cytomegalovirus, and herpes simplex.⁴ Patients with ICL may also present with malignancies. Lymphomas were among the most prevalent malignancies reported. Other viral-mediated malignancies have been identified as well. Autoimmune conditions were found in 14–23% of patients. The more-common conditions were autoimmune cytopenia and Sjögren disease.^{2,5}

PATHOGENESIS

The underlying etiology of ICL remains unclear, with several purposed mechanisms. The first hypothesis is increased T-cell apoptosis due to overexpression of Fas/CD95, which can directly transduce an apoptotic death signal on trimerization with Fas ligand. The next theory involves diminished generation of T-cell precursors. Results of studies have indicated that a defect in hematopoietic stem cells may be involved in disease progression.⁶ The third concept involves CD4 T-cell antibodies. There were more antibodies detected on CD4 cells in patients with ICL compared with normal CD4 cell populations. Defective cytokine production is postulated as playing a role in ICL because tumor necrosis factor α and interferon γ were found to be decreased in patients with ICL. Dysregulation in CXCR4 expression has been identified in cases of ICL *via* changes in the CXC chemokine *SDF-1/CXCR4* axis.^{7,8} Another model involves biochemical failure of the CD3 T-cell receptor pathway *via* p56 *Lck* kinase alteration.^{4,9} Gorska and Alam¹⁰ identified a gene mutation in *UNC119* that caused impaired activation of the tyrosine kinase *Lck*, which led to diminished T-cell responses to T cell receptor stimulation, a crucial step in the adaptive immune response, which may provide a molecular mechanism for a subset of patients with ICL.¹⁰ The variable clinical presentation of ICL strongly suggests the possibility that the disease is multifactorial and incorporates aspects from the various hypotheses.

DIAGNOSIS

ICL is a diagnosis of exclusion, and an extensive workup is needed for proper evaluation, which includes absolute CD4 and CD8 counts, B cell counts, and natural killer cell counts, immunoglobulin levels, HIV testing, and purified protein derivative tuberculosis skin test. The U.S. Centers for Disease Control and

Table 1 Conditions associated with low CD4 levels*

Autoimmune
Sjögren disease
Systemic lupus erythematosus
Kikuchi disease
Drugs
Corticosteroids
Chemotherapy
Cytotoxic immunosuppressants
Genetic syndromes
XMEN
WHIM
Unc119 mutation
Hematologic conditions
Lymphoma
Myelodysplastic syndromes
Aplastic anemia
Infections
HIV-1 and HIV-2
Human T-cell lymphotropic viruses 1 and 2
Mycobacterium tuberculosis
Epstein-Barr virus
Cytomegalovirus
Human herpes virus 6
Recalcitrant warts
Various
Common variable immune deficiency
Sarcoidosis
Radiation therapy

XMEN = X-linked magnesium deficiency with Epstein-Barr virus infection and neoplasia; WHIM = warts, hypogammaglobulinemia, infections, and myelokathexis; Unc119 = uncoordinated 119; HIV = human immunodeficiency virus.

*Adapted from a table in Ref. 9.

Prevention's diagnostic criteria require that the absolute CD4 count be <300 cells/mL or that the percentage of CD4 be <20% of the total lymphocytes. In children ages 0–23 months, the diagnosis includes a CD4 count of <1000 cells/mL; however, the diagnosis is established with a CD4 count of <300 cells/mL in children 2–12 years old.¹ Testing should be performed on at least two separate occasions, 1–3 months apart, for the most accurate results. The diagnosis is dependent on the absence of any underlying causes for a low CD4 count (Table 1).^{1,9,11} In addition, patients with ICL can be tested for OKT4 epitope deficiency, which can cause a deceptively low or absent CD4 cell count. The OKT4 is the most common antigen recognized by the monoclonal antibody used to detect CD4 cells in flow cytometry. In such cases, other antibodies should be

used to detect CD4 levels.¹² The prevalence of OKT4 in ICL is unknown.

MANAGEMENT

The first step of therapy should be aimed at treating the opportunistic infection present (when appropriate) and prophylaxis against future infections. There are no published guidelines for the treatment, monitoring, or prophylaxis of patients with ICL. Current recommendations are based on experience with patients infected with HIV.¹³ When the CD4 count drops to <200 cells/mL, TMP/SMX therapy should be initiated.^{4,9} Azithromycin therapy should be considered if the CD4 count drops to <50 cells/mL. There is no prophylactic treatment recommended for *Cryptococcus*. However, after induction and consolidation therapy for an active infection is complete, it is recommended that the patient be maintained with oral fluconazole 200 mg daily for at least 1 year. Discontinuation of fluconazole should be dependent on symptoms and CD4 level.¹⁴

Ahmed *et al.*⁴ indicated monitoring CD4 counts in patients who are stable and without signs of infection every 4 months, other investigators indicated monitoring every 6 months. Zonios *et al.*² noted that patients were at the greatest risk for subsequent infections within 2 years of their diagnosis and that patients with ICL should be followed up closely for the first 3 years. Approximately one-fifth of their study patients had resolution of their lymphocytopenia within that time frame, which allowed for the discontinuation of prophylactic medication.²

There have been several proposed methods of increasing the CD4 count with variable results. The most widely used agent is interleukin 2. There are several case reports that revealed increased CD4 counts in response to therapy.^{4,15,16} However, it is unknown whether these cells function normally. There is also a significant adverse effect profile to be concerned with when initiating interleukin 2 therapy. Other cytokines being studied are interferon γ and interleukin 7.¹⁷ There are case reports that indicate successful treatments with both therapies.^{15,16} An additional successfully used method is hematopoietic cell transplantation.¹⁶ The advantages and disadvantages of each option must be weighed when determining the best treatment course for a patient.

Answers to the Questions:

- A. False. All patients with ICL should be evaluated for prophylactic treatment. However, there are no prophylactic treatment guidelines specific to patients with ICL. The recommendations are extrapolated from patients with HIV.

- B. False. Low CD4 counts, with low or normal CD8 levels, are the most common immune system abnormalities identified in patients with ICL.
- C. True. *C. neoformans* is the most common infectious organism identified.
- D. False. The pathogenesis of ICL remains unclear.
- E. False. This disease affects patients of all ages.

Pearls

- ICL should be considered in the diagnosis of any patient with a low CD4 count and a negative HIV test result.
- ICL is a diagnosis of exclusion, but patients should have a CD4 count of <300 cells/mL or <20% total lymphocyte count in the absence of any underlying primary or secondary immune deficiency.
- Patients with ICL are considered for prophylactic therapy, depending on their CD4 counts, based on the guidelines developed for HIV.
- Patients with ICL should be monitored closely for at least 3 years after the initial diagnosis.
- The risks and benefits of CD4 count-raising agents should be weighed before initiating therapy.

Pitfalls

- ICL is a rare disorder and can be overlooked when evaluating patients with low CD4 counts; these patients require an immunologic evaluation that considers all the differential diagnoses.
- It is important to check both CD4 and CD8 levels on multiple occasions because low CD4 and CD8 levels portend a worse prognosis.
- Consider checking for *OKT4* epitope deficiency in patients with low CD4 counts because their CD4 levels may seem falsely low.
- Recurrent infections may occur if maintenance therapy for cryptococcal infections is stopped before 1 year.
- Initiating prophylactic antibiotics may help prevent opportunistic infections; however, there are no specific guidelines for this patient population.

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