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Idiopathic CD4 lymphocytopenia:

Pathogenesis, etiologies, clinical presentations and treatment strategies

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Abstract

Background—Idiopathic CD4 lymphocytopenia (ICL) is a rare condition characterized by an unexplained deficit of circulating CD4 T cells leading to increased risk of serious opportunistic infections. The pathogenesis, etiology, clinical presentation, and best treatment options remain unclear.

Objective—To describe the clinical presentation, treatment strategies, and outcome of patients with ICL seen in a single referral center.

Methods—In a retrospective study, from January 1993 to January 2014, the demographic characteristics, clinical presentation, and treatments of patients diagnosed with ICL were reviewed.

Results—Twenty-four patients (14 female [58%] and 10 male [42%]) were evaluated. The mean age was 45 ± 17.6 years (range 7–76 years). Mean CD4 and CD8 T-cell counts at the time of diagnosis were 119 ± 84/mm^3 (range 4–294/mm^3) and 219 ± 258/mm^3 (range 7–630/mm^3), respectively. Seventeen patients (71%) had opportunistic infections, 4 (17%) had malignancies, and 3 (13%) had unexplained demyelinating disease and neurologic problems. Most patients had normal levels of immunoglobulins. Thirteen patients had abnormally low to absent response to phytohemagglutinin, concanavalin A, and antigens (candida and tetanus). Three patients had resolution of warts and 1 had mycobacterial lung infection on interleukin-2 with increases in CD4 count. The 11 patients on trimethoprim and sulfamethoxazole had no further hospital admissions for infections.

Conclusion—The pathogenesis of ICL remains unclear. Although only some patients are healthy, most patients present with opportunistic infections. There is no known standard treatment aside from prophylactic antibiotics.

Introduction

Idiopathic CD4 lymphocytopenia (ICL) is an unusual disease in which there is an unexplained deficit of circulating CD4 T cells, leading to fungal, parasitic, and other serious opportunistic infections. This entity was first recognized in 1989 in patients with low CD4

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counts in the absence of human immunodeficiency virus (HIV) type 1 and 2 infections. The Centers for Disease Control and Prevention (CDC) described ICL as an absolute CD4 count lower than 300 cells/mm^3 or less than 20% of total T cells on more than 1 occasion, no evidence of infection with HIV-1 or HIV-2 or human T-cell lymphotropic virus type 1 or 2, and absence of any other known immunodeficiencies or therapies that might suppress T-cell numbers.[1–3] The characteristic clinical presentations and immunologic findings were described in studies from 1989 and 1993.[1,3–5] These patients presented with opportunistic infections such as *Pneumocystis jirovecii* pneumonia, John Cunningham viral infection, and disseminated *Cryptococcus neoformans*.[6–8] Subsequent national case series and reviews of the literature have affirmed the overall nature of this puzzling syndrome.[4,9–11] The aim of this study was to describe the clinical presentations, treatment strategies, and outcome of these patients from 1 medical center.

Methods

In this retrospective study, patients with ICL who were seen at the immunology clinic from January 1993 to January 2014 were reviewed. These patients had at least 2 confirmed absolute CD4 T-cell counts lower than 300 cell/mm^3. Patients with other immune defects or medications that could lead to lymphopenia were excluded. All patients were negative for HIV-1 and -2 and human T-cell lymphotropic virus types 1 and 2. Immunoglobulins (IgG, IgM, IgA) and T-cell proliferative response (phytohemagglutinin, concanavalin A, tetanus, and candida) were examined in some patients. Infectious history was compiled from medical records. For subjects with autoimmune or neoplastic disease, blood tests and radiologic reports were examined.

Acute treatment of opportunistic infections was given in standard doses. For prophylaxis, patients with CD4 counts lower than 200 cells/mm^3 received sulfamethoxazole and trimethoprim; for those with CD4 counts lower than 100 cells/mm^3, 1,200 mg of azithromycin weekly was added. Patients who could not tolerate azithromycin received 500 mg twice a day of clarithromycin instead. Patients with a history of herpes infections were continued on acyclovir or valacyclovir. For patients with previous fungal disease, 400 mg of fluconazole was continued. Four patients diagnosed previously were offered treatment with low-dose polyethylene glycol–modified interleukin-2 (IL-2) or IL-2 in a separately approved institutional review board study, in which subjects were given 250,000 U/m^2 by biweekly subcutaneous injections.[12]

Results

Patient Demographics

Twenty-nine patients were referred for lymphopenia, of whom 24 met the inclusion criteria for ICL. Of these,14 patients (58%) were female and 10 (42%) were male. Mean age at the time of diagnosis was 45 ± 17.6 years (range 7–76 years). None had a family history of any similar disease. Detailed demographic characteristics are listed in Table 1.

Immunologic Characteristics

Mean CD4 and CD8 T-cell counts at the time of diagnosis were 119 ± 84/mm^3 (range 4–294/mm^3) and 219 ± 258/mm^3 (range 7–630/mm^3), respectively. Serum immunoglobulin levels were normal in the 17 patients (70%) for whom levels were tested. Twelve patients had abnormally low to absent T-cell proliferative responses to phytohemagglutinin, concanavalin A, and antigens (candida and tetanus; Table 2). One patient had IgA deficiency and another patient who had other comorbidities including hepatitis B and mixed connective tissue disease had significantly increased IgG (2,700 mg/dL) and IgA (956 mg/dL) levels (Table 2).

Clinical Presentations

Eighteen patients (75%) had opportunistic infections, 10 (41%) had malignancies, 5 (20%) had autoimmunity, and 3 (13%) had unexplained demyelinating or other neurologic disease. For infections, the most common were papilloma infections leading to skin or mucosal warts (n = 5), invasive herpes (n = 3), and tuberculosis or other mycobacterial infections (n = 3). Two patients had cryptococcal meningitis, 1 had cryptococcal osteomyelitis, and 1 presented with cryptococcal skin infection. Only 1 patient had a history of *P jirovecii* infection (Table 3). Three patients were disabled from work because of multiple hospital admissions and recurrent infections. Five patients (21%) had lymphoma (2 with non-Hodgkin lymphoma, 1 with Hodgkin lymphoma, and 1 with primary leptomeningeal lymphoma). Five patients had solid tumor tumors (prostate cancer, papillary thyroid cancer, colon cancer, skin squamous cell carcinoma, and pituitary adenoma). Five subjects had autoimmunity, including immune thrombocytopenia, hemolytic anemia, Sjögren syndrome, systemic lupus, and lichen planus, and 3 others had unclear neurologic disease.

Treatments and Interventions

Treatment options for patients with ICL were classified into 4 general groups (Table 4):

Group 1: No treatment—Three patients with CD4 cell counts higher than 230 but lower than 300/mm^3 were stable and required no antibiotic medication. One of these patients had Sjögren syndrome and was noted to have lymphopenia on routine workup. One had neuropathy and *Molluscum contagiosum* and the third patient had thyroid cancer but reported no other disease.

Group 2: Treated with trimethoprim and sulfamethoxazole + fluconazole or azithromycin—Eighteen patients had received trimethoprim and sulfamethoxazole but only 11 were maintained on this medication. None of these patients further required hospitalizations. One patient with a CD4 count of 280/mm^3 was started on trimethoprim and sulfamethoxazole for sinusitis, urinary tract, and dental infections. Antibiotic treatment decreased her infections and over a period of 10 years her CD4$^+$ T-cell count increased to more than 700 mm^3, resulting in discontinuation of antibiotic treatment.

Group 3: IL-2 therapy with or without antibiotics—Four patients were started on polyethylene glycol–modified IL-2 or IL-2 given subcutaneously. Three patients in this group had severe resistant cutaneous or venereal warts that did not respond to standard

treatments. In each case, warts subsided after starting IL-2. In 1 patient, the CD4 cell count increased from 188 to 343 mm^3 after receiving IL-2. In the fourth patient who had bronchiectasis and chronic mycobacterial disease, IL-2 led to long-term respiratory stabilization with clearance of mycobacteria. Fatigue was the most common side effect of this therapy and was observed in 50% of patients.

Group 4: Intravenous immunoglobulin—Three patients had been treated with intravenous immunoglobulin, given for concomitant demyelinating polyneuropathy in 2 and autoimmune hemolytic anemia in 1. This patient had a history of immune thrombocytopenia before presentation with severe venereal warts.

Discussion

This article describes the clinical and immunologic characteristics of 24 patients with ICL, a rare disease of unknown etiology. These patients had mean age of 45 years (range 7–76 years) similar to the original CDC report (mean age 43 years, range 17–78 years).[2,3] The results also are similar to the age range of recent reports (25–85 years old for 39 subjects and 19–70 years old for 40 subjects).[11,13] The CDC report noted a male-to-female ratio of 29:18 that differed from our patient population (male-to-female ratio 10:14; Table 1).[3]

The cause of this syndrome remains unclear; family histories are indeterminate.[11] Genetic etiologies have not been identified in most, although in a few outliers, lymphocyte-specific kinase, uncoordinated 119, IL-2–inducible T-cell kinase deficiency, and heterozygous RAG1 have been reported as causative in a few rare patients.[14–19]

As in other reports, opportunistic infections were the most common clinical manifestation in our patients and, in most cases, the reason for diagnosis. The infections observed were similar to those of previous reports, including cryptococcal, human papilloma virus, herpes virus, hepatitis virus, tuberculosis, John Cunningham virus, and *P jirovecii* infection.[1,3,4,8,9,20–25] *Cryptococcus neoformans* meningitis has been reported previously and was seen in 2 of our patients; cryptococcal osteomyelitis of the rib in another patient was the presenting symptom of the immune defect, as reported previously.[8,9,11,26] One of the most common infections observed in our patient population was human papilloma virus mucocutaneous lesions, also described in a French group.[11] In patients with HIV infection, *P jirovecii* pneumocystis pneumonia is more likely to occur in patients with a $CD4^+$ T-lymphocyte count lower than 200/μL.[27] Although the mean $CD4^+$ T-lymphocyte counts in our patients was 119 ± 84/mm^3, pneumocystis pneumonia was seen in only 1 patient, similar to other reports, but in contrast to the higher prevalence in the first reported series.[3,11]

As previously noted, although the low CD4 T-cell numbers garner the most attention, more than half our patients had low numbers of $CD8^+$ T cells and natural killer cells. As in previous studies, these cells were defective in function, with decreased proliferative response to phytohemagglutinin, concanavalin A, and recall antigens.[10,11] Prior studies have shown that these patients with low CD4 and $CD8^+$ T-cell counts present with more severe opportunistic infections.[28] In addition, studies have shown that acute and chronic infections

can result in depletion of $CD4^+$ T lymphocytes and $CD8^+$ T lymphocytes, which also could contribute to lymphopenia.

Lymphoma, mostly non-Hodgkin lymphoma, and solid tumors were observed in 41% of our patients, which is significantly higher than what was reported by Regent et al[11] (17.5%). Five of the 24 patients (22%) had autoimmune syndromes as noted in other series.[11,29]

Treatment options for ICL have focused on treating acute and preventing opportunistic infections. Our patients were managed in 4 general groups based on guidelines used for patients with HIV.

Prophylaxis Treatment Guideline

- Patients with CD4 counts lower than 200 cells/mm^3 received sulfamethoxazole and trimethoprim; for those with CD4 counts lower than 100 cells/mm^3, 1,200 mg of azithromycin weekly was added.
- Subjects with a history of herpes infections were continued on acyclovir or valacyclovir.
- Patients with low levels of $CD4^+$ and $CD8^+$ cells received anti-fungal treatment. This is because a higher incidence of disseminated cryptococcal infections has been observed in patients with ICL who have low levels of $CD4^+$ and $CD8^+$ cells.[13]

We treated 4 patients with polyethylene glycol–modified IL-2 or IL-2 in a separately approved institutional review board study, in which subjects were given 250,000 U/m^2 by biweekly subcutaneous injections. Three of these had resistant wart infections; a fourth had long-term IL-2 treatment for pulmonary mycobacterial infection, which completely resolved.[12,30] Regent et al[11] treated 6 patients with IL-2 and observed that patients with responses to IL-2 treatment in vivo showed improved lymphocyte counts.[11] Long-term IL-2 also has been used as successful management of cytomegalovirus retinitis in ICL.[31] Other studies have reported success with recombinant IL-2 with or without interferon-γ.[22,30,32,33] IL-7 also has attracted attention, because impaired CD4 T-cell responses to IL-7 in ICL might contribute to cell depletion[34]; this cytokine was used in an open-label phase I and IIa clinical trial and 1 case of progressive multifocal leukoencephalopathy in ICL, with some benefit.[35,36] The choice of subjects for cytokine therapy and the parameters to be used for follow-up are unclear and further studies would be required to evaluate efficacy.

In summary, ICL has unclear etiology and is most commonly seen in adults who present with unusual infections, spurring the discovery of very low CD4 T cells. Most also have deficient CD8 T and natural killer cells, and when investigated, lymphocyte proliferation is impaired. Current management includes prophylactic antibiotics, particularly when the $CD4^+$ cell counts are lower than 200/mm^3.

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Table 1

Demographics Characteristics of Patients With Idiopathic CD4 Lymphocytopenia

	Patients, n (%)
Sex	
Male	10 (42)
Female	14 (58)
Age (y)	
0–10	1 (4)
11–20	0 (0)
21–30	5 (21)
31–40	6 (25)
41–50	2 (8)
51–60	5 (21)
61–70	5 (21)
Race	
Caucasian	18 (75)
African American	3 (13)
Asian	2 (8)
Hispanic	1 (4)

Table 2

Initial T-cell Numbers, Functions, and Immunoglobulin Levels[a] in the 24 Patients Reviewed

Patient	CD3	CD4	CD8	B cells	PHA	Con A	Antigens	IgG	IgA	IgM
1	81	60	31	53	L	L	N	—	—	—
2	396	273	252	48	N	N	N	1,320	184	146
3	416	188	234	—	L	L	A	830	67	74
4	221	230	102	33	N	N	L	544	89	143
5	797	160	140	—	N	N	L	933	202	115
6	—	74	59	—	N	L	L	1,141	139	136
7	105	27	27	121	L	L	L	1,380	183	196
8	991	120	69	—	L	L	L	703	7	350
9	237	32	26	34	L	L	L	1,540	134	133
10	279	103	145	—	—	—	—	2,700	956	114
11	241	87	145	—	L	N	L	1,980	293	107
12	—	29	—	—	—	—	—	—	—	—
13	—	230	630	—	N	N	A	1,060	295	165
14	—	197	51	—	N	N	N	N	N	N
15	—	80	547	—	N	L	N	970	179	118
16	—	294	246	—	N	N	N	1,450	186	149
17	53	4	7	30	—	—	—	1,160	248	77
18	—	37	57	274	—	—	—	1,082	135	95
19	505	89	391	129	L	L	L	—	—	—
20	315	186	111	25	—	—	—	—	—	—
21	1,261	142	1,088	106	—	—	—	2,900	213	181
22	65	21	4	274	—	—	—	—	—	—
23	—	113	444	22	—	—	—	2,440	960	225
24	337	82	228	92	—	—	—	1,759	153	74

Abbreviations: A, absent; Con A, concanavalin A; Ig, immunoglobulin; L, low; N, normal; PHA, phytohemagglutinin.

[a]Normal adult ranges: CD3 750–2,500/mm^3; CD4 480–1,700/mm^3; CD8 = 180–1,000/mm^3; B = 75–375/mm^3; IgG 768–1,728 mg/dL; IgA 99–396 mg/dL; IgM 28–266 mg/dL.

Table 3

Clinical Presentations in the 24 Patients Reviewed

	Patients, n (%)
Infections (75%)	
Viral	
Human papilloma virus	5 (21)
Herpes meningoencephalitis, disseminated herpes, esophagitis	3 (13)
Hepatitis	2 (8)
Progressive multifocal leukoencephalopathy (JC virus)	1 (4)
TB or mycobacterium	3 (13)
Parasites—*Pneumocystis jirovecii* pneumonia	1 (4)
Fungal	
Oral, skin, vaginal candida	4 (17)
Cryptococcal meningitis, osteomyelitis	4 (17)
Fungal toe nail	2 (8)
Neoplasm (40%)	
Leptomeningeal lymphoma	1 (4)
Hodgkin lymphoma	1 (4)
Non-Hodgkin lymphoma	3 (12)
ACTH secreting adenoma	1 (4)
Prostate cancer	1 (4)
Thyroid cancer	1 (4)
Colon cancer	1 (4)
Invasive squamous cell carcinoma	1 (4)
Autoimmunity (21%)	
ITP, hemolytic anemia	1 (4)
Sjögren syndrome	2 (8)
Systemic lupus	1 (4)
Lichen planus	1 (4)
Neurologic disease (13%)	
Subacute inflammatory demyelinating polyradiculoneuropathy	2 (8)
Neuropathy	1 (4)

Abbreviations: ACTH, adrenocorticotropic hormone; ITP, immune thrombocytopenia; JC, John Cunningham; TB, tuberculosis.

Table 4

Treatment Options in 4 Groups of Patients With Idiopathic CD4 Lymphocytopenia

CD4 count	Clinical manifestations	Treatment
Group 1: no treatment		
273	thyroid cancer	none
230	neuropathy, *Molluscum contagiosum*	none
294	skin fungal infection	none
Group 2: trimethoprim and sulfamethoxazole + fluconazole or azithromycin		
4	corneal herpes zoster, HPV, recurrent vaginal candidiasis, UTIs	trimethoprim and sulfamethoxazole + dapsone + azithromycin + Valtrex
21	genital warts, HPV, *Molluscum* sp, candidiasis	trimethoprim and sulfamethoxazole + azithromycin + fluconazole
32	cryptococcal meningitis	trimethoprim and sulfamethoxazole + fluconazole + clarithromycin
37	chronic herpetic lesions	trimethoprim and sulfamethoxazole + fluconazole + azithromycin
60	cryptococcal meningitis	trimethoprim and sulfamethoxazole + fluconazole
74	bacterial pneumonia, fungal infection	trimethoprim and sulfamethoxazole + azithromycin
80	cryptococcal skin infections	trimethoprim and sulfamethoxazole + fluconazole
82	bronchitis, otitis, folliculitis	trimethoprim and sulfamethoxazole + acyclovir + steroid
89	pneumonia	trimethoprim and sulfamethoxazole
103	neurological disease	trimethoprim and sulfamethoxazole
113	lymphoma	trimethoprim and sulfamethoxazole
120	nail fungal, thrombophlebitis	trimethoprim and sulfamethoxazole
142	MAC and *Pneumocystis jirovecii* pneumonia	trimethoprim and sulfamethoxazole
186	herpes simplex esophagitis	trimethoprim and sulfamethoxazole + azithromycin + valacyclovir
197	chronic persistent plantar warts, EBV infection	trimethoprim and sulfamethoxazole + fluconazole
Group 3: IL-2 ± antibiotics		
27	cryptococcal osteomyelitis	IL-2 + trimethoprim and sulfamethoxazole + azithromycin
29	*Mycobacterium gordonae,* bronchiectasis	IL-2
87	venereal warts, anemia, ITP	IL-2 + IVIG + fluconazole
188	severe warts	IL-2 + trimethoprim and sulfamethoxazole
Group 4: IVIG		
87	ITP, venereal wart, anemia	IVIG + IL-2 + fluconazole
160	CIPD	IVIG + trimethoprim and sulfamethoxazole
230	CIPD, erythema multiform	IVIG + hydroxychloroquine

Abbreviations: CIPD, chronic inflammatory demyelinating polyneuropathy; EBV, Epstein-Barr virus; HPV, human papillomavirus; IL-2, interleukin-2; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; MAC, mycobacterium avium complex; UTI, urinary tract infection.