INTERNAL MEDICINE

□ CASE REPORT □

Multiple Immune Abnormalities in a Patient with Idiopathic CD4+ T-Lymphocytopenia

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Abstract

Idiopathic CD4+ T-lymphocytopenia (ICL) is a new disease entity characterized by CD4+ T-lymphocyte depletion without evidence of HIV infection. We report a 27-year-old ICL patient with a long history of multiple immune abnormalities. His CD4+ T-lymphocyte count started to decrease after generalized lymphadenopathy of an unknown cause at age 3. He satisfied the criteria for ICL at age 9, and the decreased CD4+ T-lymphocyte count persisted for more than 18 years. This is probably the first childhood-onset ICL case in which the trigger event for the development was known together with the patient's autoimmune background.

Key words: ICL, CD4, T lymphocytopenia

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Introduction

Idiopathic CD4+ T-lymphocytopenia (ICL) is a rare syndrome that was first reported in 1992 by the Centers for Disease Control and Prevention (CDC) of the USA (1). In the same year, a similar case was also reported in Japan (2). This disease is characterized by an absolute decrease in CD 4+ T lymphocyte count to less than 300/μL or to less than 20% of total T lymphocytes without evidence of human immunodeficiency virus-1 (HIV-1), HIV-2, human T-cell leukemia virus type-1 (HTLV-1), or HTLV-2 infection, a known immunodeficiency syndrome, or therapy-related CD4+ T-lymphocyte depression (3-8). ICL is a cluster of heterogeneous diseases with diverse clinical courses and immunologic characteristics. Although some patients present with opportunistic infections such as cryptococcosis, human papillomavirus (HPV), and nontuberculous mycobacteria, others remain in a relatively healthy condition for years (8). Since the prognosis of ICL has not been well defined, a prospective study to evaluate the history of this disease was performed. Thirty-nine cases were collected, and the details of the study were reported recently (8). Here, we report a unique ICL patient with childhood onset and a long history of multiple immune abnormalities.

Case Report

A 27-year-old man was referred to our hospital because of hypoproteinemia with monoclonal gammopathy. The patient showed no remarkable findings on physical examination except for redness of the face and conjunctival hyperemia. He was in good physical condition with a good appetite, but his serum total protein was very low due to hypoalbuminemia (Table 1). No protein was detected in his urine. His immunoglobulin levels were nearly normal, but he had a small amount of IgA-kappa monoclonal immunoglobulin; i.e., monoclonal gammopathy of undetermined significance (MGUS). There was no sign of liver dysfunction or renal dysfunction, and his serum levels of asparate-aminotransferase (AST), alanine-aminotransferase (ALT), blood urea nitrogen (BUN), and creatinine were all within the appropriate reference range. In a peripheral blood examination, he was found to be polycythemic (Table 1). Al-

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Table 1. Routine Laboratory Data

Hematologic		Serum chemistry	
Red blood cells	6.02×10^6/μL	Total protein	5.5 g/dL
Hemoglobin	18.4 g/dL	Albumin	2.7 g/dL
Leukocytes	5,600 /μL	IgG	1,140 mg/dL
Neutrophils	81%	IgA	344 mg/dL
Lymphocytes	12% (672 /μL)	IgM	147 mg/dL
Monocytes	4%	Na	136 mEq/L
Eosinophils	3%	K	4.0 mEq/L
Platelet	17.6×10^4/μL	Cl	105 mEq/L
		BUN	12 mg/dL
Flow-Cytometric		Creatinine	0.78 mg/dL
CD3	46.8% (314 /μL)	Total bilirubin	0.4 mg/dL
CD4	7.5% (50 /μL)	AST	21 IU/L
CD8	40.2% (270 /μL)	ALT	33 IU/L
CD22	6.9% (46 /μL)	LD	151 IU/L
CD16	43.2% (290 /μL)	Anti-HIV antibody	(-)
CD25	6.4% (43/μL)	Anti-HTLV-1 antibody	(-)
CD56	43.1% (290 /μL)	Anti-nuclear antibody	(-)
		Anti-CMV antibody	
		IgG	7,600
		IgM	0.6

BUN: blood urea nitrogen, AST: asparate-aminotransferase, ALT: alanine-aminotransferase, LD: lactic dehydrogenase, CMV: cytomegalovirus

though his white blood cell count was normal at 5,600/μL, his absolute lymphocyte count was very low at 672/μL. A lymphocyte subset analysis indicated a marked decrease in his absolute CD4+ T-lymphocyte count to only 50/μL (Table 1 and Fig. 1). His absolute B-lymphocyte count was also low at 43/μL, but natural killer cell compartment was well preserved (Table 1 and Fig. 1). Serum tests for HIV-1, HTLV-1 and anti-nuclear antibody (ANA) were negative. He had a very high anti-cytomegalovirus (CMV) IgG antibody titer with negative IgM antibody indicating past CMV infection (Table 1).

A review of his medical records showed that he had a long history of immune abnormalities (Fig. 2), although his family history was not significant. There was no consanguineous marriage. First, he developed autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) at age 1, which was successfully treated with prednisolone. Next, he developed measles pneumonia at age 3 and then suffered from repeated episodes of generalized lymphadenopathy with polyclonal hypergammaglobulinemia (IgG: 3,000-6,000 mg/dL) from ages 3 to 9. Rheumatoid arthritis test (RA test) was positive suggesting an autoimmune background. The result of Epstein-Barr virus (EBV) antibodies (VCA-IgG positive, VCA-IgM negative and EBNA positive) indicated the past EBV infection. The size of the lymph nodes was as large as 4 cm in diameter, but biopsies of the lymph nodes revealed reactive lymphadenitis. Analysis of his peripheral blood lymphocyte subsets was performed at age 4, and an inversion of the CD4/CD8 ratio was noticed. His absolute lymphocyte count including CD4+ T-lymphocytes decreased gradually, and he satisfied the criteria for ICL at age 9. A serum test for HIV was negative. At age 12, he developed cryptococcal pneumonia, which was successfully treated with fluconazole. At age 14, he developed mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach with multiple swelling of abdominal lymph nodes, which gradually regressed within several years without therapy. His serum total protein started to decrease from age 15 and never returned to the normal level. He suffered a recurrence of his ITP at age 17 and developed thrombotic thrombocytopenic purpura (TTP) at 20, which were successfully treated with a short course of prednisolone and steroid pulse therapy with plasma exchange, respectively. He became polycythemic after recovering from these episodes, and his RBC count exceeded 600×10^4/μL. His serum erythropoietin was slightly higher than the normal upper limit at 37.5 mU/mL (reference range: 8-36 mU/mL). Since then, he has not experienced any serious diseases that required hospitalization and has dropped out of follow-up.

Discussion

In a nationwide study of ICL in the USA, 57 patients were recruited between 1992 to 2006 (8). Eighteen patients were excluded from the study because they did not fulfill the criteria for the definition of ICL (1, 5). The excluded patients had a CD4 T-lymphocyte count of more than 300/μL, HIV antibody, or were complicated with hematological malignancies that could have caused lymphocytopenia (8). One patient was excluded because of an alternative diagnosis

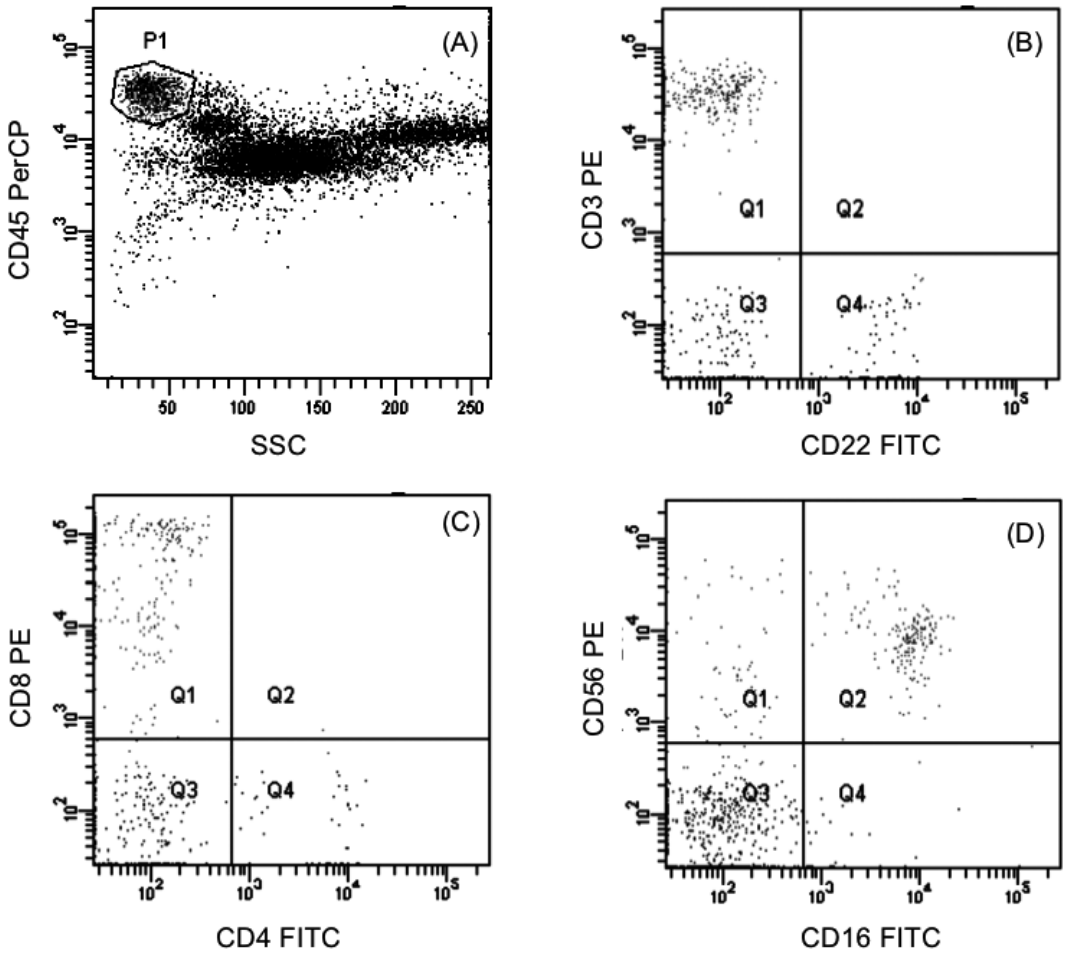

Figure 1. **Lymphocyte subset analysis of the peripheral blood. Cells were stained with various combinations of fluorescein isothiocyanate (FITC), phycoerythrin (PE), or peridinin-chlorophyll-protein (PerCP)-conjugated murine monoclonal antibodies, and the results of gated cells of figure (A) (lymphocyte population: low SSC with high CD45 antigen expression) are shown in figures (B), (C) and (D). Marked decreases in CD4+ T-lymphocytes and CD22+ B-lymphocytes are shown.**

(common variable immunodeficiency). The present patient does not meet the criteria for any known immunodeficiency diseases other than ICL. Severe combined immunodeficiency (SCID) was ruled out, and humoral immunodeficiencies such as common variable immunodeficiency and hyper-IgM syndrome were also ruled out because of his normal immunoglobulin class levels. Wiskott-Aldrich syndrome and ataxia telangiectasia were ruled out by the absence of their characteristic clinical features and laboratory data.

ICL usually occurs in middle-aged or elderly adults, and the number of patients aged from 20 to 30 years old in the cohort study was only 2 out of 39 cases (5.1%), and there were no patients younger than 20 years old (8). The present patient met the criteria for ICL from age 9. Childhood ICL cases are rare although there have been a few reports (9, 10). There is no common feature of childhood ICL, and there is heterogeneity even within childhood cases; two cases showed IgA deficiency with progressive pulmonary infection and another case showed a significant increase in γδTCR-bearing T cells (9, 10). In the present case, if we consider his peculiar past history including the development of autoimmune diseases at age 1 and recurrent episodes of lymphadenopathy from age 3, it is possible that he possessed genetic defects that led to immunodeficiency. Alternatively, the prolonged and intermittent use of prednisolone to control these episodes may have influenced or accelerated the development of ICL. ICL cases are divided into 2 subgroups in terms of their CD8+ T-lymphocyte levels: those with levels lower than the lowest 2.5% of the CD8+ T-lymphocyte counts in the control population (<180/μL) and those with levels higher than that. Since the absolute CD8+ T-lymphocyte count of this patient was 270/μL, he was classified into the latter group. In the cohort study, 5 patients (13.8%) developed AIDS defining clinical conditions during the first 24 months of observation (8). The present patient has not met the criteria for such conditions in spite of the very long follow-up duration. The most common infection in ICL is cryptococcal infection, and this patient also experienced cryptococcal pneumonia; however, that is not an AIDS defining clinical condition (11). Autoimmunity is also common in ICL, and 9 patients (23.1%) developed autoimmune diseases in the cohort study, either before diagnosis or in the follow-up period (8). One patient developed autoimmune hemolytic anemia, as in our patient, but no patient de-

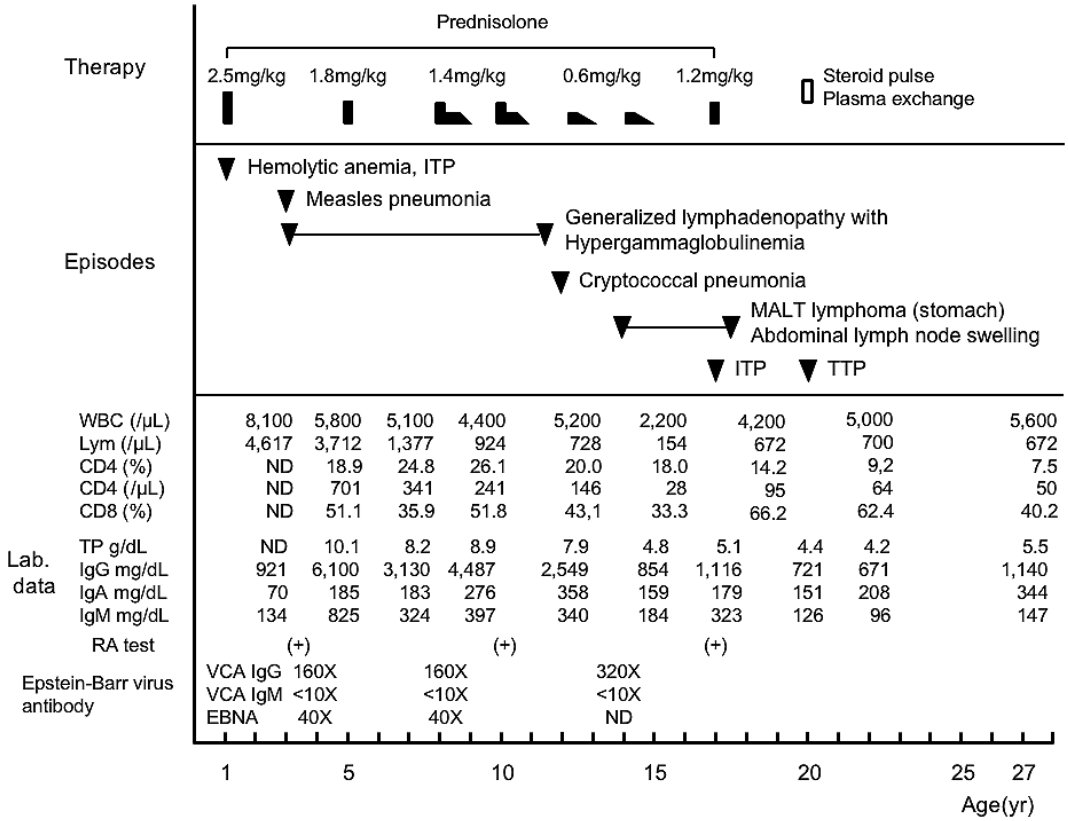

Figure 2. **Clinical course and laboratory data. ITP: idiopathic thrombocytopenic purpura, TTP: thrombotic thrombocytopenic purpura, MALT: mucosa-associated lymphoid tissue, TP: total protein, RA test: rheumatoid arthritis test, VCA: viral capsid antigen, EBNA: Epstein-Barr virus nuclear antigen**

veloped ITP. Hypoalbuminemia was one of the characteristic features of this patient. There may be some association between poor nutritional state and CD4+ T-lymphocytopenia, as suggested in very elderly people (12). It has also been reported that 6 of 103 chronic obstructive pulmonary disease (COPD) patients examined (5.8%) showed ICL, and there was a positive correlation between serum albumin level and CD4+ T-lymphocyte count (13). Among the unique features observed in this patient, the most characteristic feature was his long-term survival in spite of an extremely low CD4+ lymphocyte count. As for the prophylaxis to prevent opportunistic infections, the cohort study suggested that it should only be considered for the subsets of ICL patients with the worst prognoses, such as those with low CD8 counts or patients presenting with an AIDS defining condition (8). The present patient did not receive any prophylaxis for more than 7 years. Although the presence of anti-CD4+ lymphocyte antibody and overexpression of Fas/CD95 with enhanced apoptosis have been reported in some cases (14, 15), the etiology of ICL is still largely unknown. Further accumulation of ICL or ICL-like cases, especially childhood cases, is desired for its etiological classification and for the development of effective therapies against ICL.

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