Elevated levels of activated CD4 T cells in common variable immunodeficiency: association with clinical findings

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ABSTRACT

Background. Common variable immunodeficiency (CVID) is a very heterogeneous syndrome defined by impaired immunoglobulin production. The primary defect remains unknown, but many reports describe peripheral blood T and B lymphocyte dysfunctions in a substantial proportion of CVID patients. Immunophenotypic alterations on memory B lymphocytes correlate with clinical findings. A B-cell-oriented classification principle of the patients has been proposed.

Methods and results. We investigated the expression of activation surface molecules on CD4 and CD8 T-cells from 14 patients with CVID, 6 non-CVID hypogammaglobulinemic patients with recurrent infections, 47 asymptomatic HIV-positive patients without AIDS defining conditions and 23 healthy subjects. Lymphocyte subsets were analysed by three-colour flow cytometry. Monoclonal panel: CD38-FITC/HLADR-PE/CD4 or CD8-PerCP. In CVID patients serum levels of CD4 T-cells co-expressing the activation marker HLA-DR [CD4+ DR + (34 %), CD4+ CD38+ DR+ (18 %)] were significantly elevated compared with controls. Significant increases in CD8+ DR+ (54 %), CD8+ CD38+ (43 %) and CD8+ CD38+ DR+ (29 %) T-cells were observed in comparison with healthy controls. CVID patients with splenomegaly, lower pre-infusion IgG levels (< 600 mg/dl), autoimmune or lymphoproliferative conditions demonstrated even higher levels of CD4+ CD38+ DR+ T cells (22, 22, 21 and 21 % respectively) compared with other CVID patients (13, 13, 15 and 15 % respectively).

Conclusion. These findings indicate a state of ongoing T lymphocyte activation which is associated with clinical findings frequently observed in CVID.

Key words: Immunodeficiency. Common variable immunodeficiency. CD4. Lymphocyte activation. Classification.

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INTRODUCTION

Common variable immunodeficiency (CVID) is the most clinically relevant primary antibody deficiency in the adult age[1-2]. Hypogammaglobulinemia and defective antibody production are the hallmark of CVID syndrome, predisposing patients to recurrent bacterial infections. An increased frequency of lymphoproliferative disease, splenomegaly, granulomatosis and or autoimmune diseases is also observed in CVID patients[1-3]. Many reports describe peripheral blood T and B lymphocyte dysfunctions in a substantial proportion of CVID patients[4-5]. Recent studies

point toward defects at various stages of B-cell differentiation in CVID subgroups and support the value of a B-cell-oriented classification principle[6-12]. A good correspondence between a low number of memory B cells and splenomegaly, lymphoid proliferation, granulomatous disease and/or autoimmune diseases has been suggested[6-12]. In this study, we investigated if the alterations in peripheral T-cell activated lymphocyte subsets correlated with clinical findings in CVID patients.

MATERIAL AND METHODS

In a transversal descriptive study we analyzed activated CD4+ and CD8+ T cell-subset percentages in 14 CVID patients (21-68 years old, mean age 37.4 years, 8 men and 6 women). All patients had been diagnosed as having CVID based on diagnostic criteria for primary immunodeficiencies[13]. The clinical characteristics of the patients are summarized in table I. At the time of the immunological study all the patients were receiving substitutive therapy with intravenous immunoglobulin (IVIG), at a dose of 400 mg/kg every 3 weeks. Blood samples were obtained immediately before IVIG administration. Increased levels of lymphocyte activation markers can be observed during chronic infections. For that reason, in this study we compared the percentages of lymphocyte activated subsets in CVID patients with the percentages observed in 47 asymptomatic HIV-positive patients whithout clinical criteria of AIDS; and with 6 non-CVID hypogammaglobulinemic patients who had chronic bacterial infections and who were receiving IVIG. We also compared lymphocyte subsets percentages in CVID patients against values observed in a health control group composed of 23 healthcare workers. Splenomegaly and lymphoid proliferation were confirmed by computed tomography. Increased catabolism of serum IgG antibodies was suspected in those patients that did not reached IgG levels greater than 600 mg/dl despite conventional dosis of IVIG. None of the patients had protein losing diseases. Patients with acute infections or opportunistic infections were not included in the study.

Activated CD4 and CD8 T-cell subsets were quantitated by three color flow cytometry (FACScan, Becton & Dickinson, San Jose, CA, USA). We enumerated T-cell subsets using FITC/PE/PerCP combinations of CD38/HLA-DR/CD4 or CD8 and isotype controls. Percentages of activated CD4 and CD8 T cell subsets are expressed as a percentage of total CD4 and CD8 lymphocytes. Details of adquisition and analysis of lymphocyte subsets have been reported elsewere[14]. T-cell activated percentages were compared between groups using the non-parametric Mann-Whitney test.

Table 1

Summary of clinical characteristics of 14 CVID patients

Patient N.º	Infections	Splenomegaly	Autoinmune diseases	Lymphoid proliferation	IgG hipercatabolism
1	B,G,GI,O,P,S	+	+ (CD)	+	+
2	P,C	+	–	–	–
3	P,G, GI	–	–	+	–
4	GI	–	+ (AHA)	+	–
5	P, GI, S, C	–	–	–	–
6	P, GI	–	+ (ITP)	–	–
7	P	+	+ (AD)	+	+
8	P, GI	–	–	–	–
9	S, O, G	+	–	+	+
10	P, S, GI	–	–	+	+
11	B, P	–	–	–	–
12	–	–	+ (ITP)	–	–
13	P, S	–	–	–	–
14	P	–	–	–	–

B: bronchitis; G: giardiasis; GI: gastrointestinal; O: otitis; P: pneumonia; S: sinusitis; C: conjunctivitis; CD: celiac disease; AHA: autoimmune hemolytic anemia, ITP: idiopathic thrombocytopenic purpura; AD: autoimmune diabetes.