ORIGINAL ARTICLE

Analysis of Class-Switched Memory B Cells in Patients with Common Variable Immunodeficiency and Its Clinical Implications

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Abstract

Background: Common variable immunodeficiency (CVID) comprises a heterogeneous group of primary immunodeficiency disorders characterized by hypogammaglobulinemia leading to recurrent infections. Some patients with CVID are more susceptible to earlier onset of respiratory disease and bronchiectasis. It has been suggested that memory B cells, characterized by CD27 expression, can be used as a means to classify subsets of CVID patients.
Objective: The aim of this study was to classify a sample of Iranian patients with CVID by quantification of peripheral blood memory B cells and immature B cells and to assess the relationship between this classification and the clinical characteristics of the patients.
Methods: The study included 29 patients with CVID and 20 healthy controls. Patients were grouped as follows, according to the quantification of peripheral memory B cells: group I had less than 0.4% switched memory B cells ($CD27^+$, immunoglobulin [Ig] M^-, IgD^-) in peripheral blood lymphocytes (PBL), while in group II switched memory B cells represented more than 0.4% of PBL. Group I patients were further subdivided into groups Ia and Ib according to the proportion of $CD21^-$ peripheral B cells. The clinical and laboratory findings for the patients were then compared among the 3 groups.
Results: The percentage of switched memory B cells ($CD27^+IgM^-IgD^-$ cells in peripheral B lymphocytes) was markedly reduced in CVID patients compared with controls ($P < .001$). This percentage was less than 0.4% (group I) in 20 patients (69%) ($P < .05$). In the remaining 9 patients (group II) and all healthy controls, the percentage was greater than 0.4%. Bronchiectasis was more frequent in group I than group II ($P < .05$). Following subdivision of group I patients into groups Ia and Ib based on $CD21^-$ peripheral B cells, the rate of autoimmunity was found to be much higher in group Ia than group Ib.
Conclusions: CVID patients with reduced numbers of switched memory B cells are more prone to recurrent respiratory infections and development of bronchiectasis, and as such, need more special care than other CVID patients. Thus, classification of CVID patients by assessment of switched memory B cells could help physicians to predict clinical prognosis of these patients.

Key words: Common variable immunodeficiency. Classification. Clinical manifestation. Switched memory B cells. Bronchiectasis.

Resumen

Antecedentes: La inmunodeficiencia variable común (IVC) comprende un grupo heterogéneo de trastornos de inmunodeficiencia primarios caracterizados por hipogammaglobulinemia que genera infecciones recurrentes. Algunos pacientes con IVC son más susceptibles a la aparición más temprana de enfermedad respiratoria y bronquiectasia. Se ha sugerido que los linfocitos B memoria, caracterizados por la expresión de CD27, pueden usarse como método de clasificación de subgrupos de pacientes con IVC.
Objetivo: El objetivo de este estudio fue clasificar una muestra de pacientes iraníes con IVC mediante la cuantificación de los linfocitos

B memoria de sangre periférica y linfocitos B inmaduros y valorar la relación entre esta clasificación y las características clínicas de los pacientes.
Métodos: Participaron en el estudio 29 pacientes con IVC y 20 sujetos control sanos. Los pacientes se agruparon como sigue, según la cuantificación de los linfocitos B memoria en sangre periférica: el grupo I tenía menos de un 0,4% de linfocitos B memoria con cambios ($CD27^+$, Ig M^-, IgD^-) en los linfocitos de sangre periférica (LSP), mientras que en el grupo II los linfocitos B memoria con cambios representaban más de un 0,4% de los LSP. Los pacientes del grupo I se subdividieron en dos grupos, Ia y Ib según la proporción de linfocitos B periféricos $CD21^-$. A continuación se compararon los resultados clínicos y analíticos de los pacientes entre los tres grupos.
Resultados: El porcentaje de linfocitos B memoria con cambios (células $CD27^+IgM^-IgD^-$ en linfocitos B periféricos$^-$) fue notablemente inferior en los pacientes con IVC comparado con los controles ($P < 0,001$). El porcentaje fue de menos de un 0,4% (grupo I) en 20 pacientes (69%) ($P < 0,05$). En el caso de los nueve pacientes restantes (grupo II) y todos los controles sanos, el porcentaje fue superior al 0,4%. La bronquiectasia fue más frecuente en el grupo I que en el grupo II ($P < 0,05$). Tras la subdivisión de los pacientes del grupo I en los grupos Ia y Ib basándonos en los linfocitos B periféricos $CD21^-$, se observó que la proporción de autoinmunidad fue mucho más elevada en el grupo Ia que en el Ib.
Conclusiones: Los pacientes con IVC con número reducido de linfocitos B memoria con cambios son más propensos a padecer infecciones respiratorias recurrentes y a presentar bronquiectasia y, en consecuencia, necesitan más cuidados especiales que otros pacientes con IVC. Por lo tanto, la clasificación de los pacientes con IVC mediante el recuento de los linfocitos B memoria con cambios podrían ayudar a los facultativos a predecir el pronóstico clínico de estos pacientes.

Palabras clave: Inmunodeficiencia común variable. Clasificación. Manifestación clínica. Linfocitos B memoria con cambios. Bronquiectasia.

Introduction

Common variable immunodeficiency (CVID) is a heterogeneous group of primary immunodeficiency disorders characterized by hypogammaglobulinemia and impaired antibody production [1]. Patients with CVID experience recurrent bacterial infections, most notably of the upper and lower respiratory tract and gastrointestinal tract [1,2]. In addition to infectious complications, autoimmune diseases and lymphoma are relatively common in these patients [3,4]. Diagnosis of CVID is based on standard criteria: decreased serum immunoglobulin (Ig) concentrations of at least 2 isotypes and genetic exclusion of other antibody deficiencies associated with well-defined single-gene defects such as X-linked agammaglobulinemia [5], hyper-IgM syndromes [6], and X-linked lymphoproliferative syndrome [7].

It has been shown that some groups of patients with CVID are particularly susceptible to earlier onset of respiratory diseases and bronchiectasis [8], while others display only mild to moderate clinical manifestations. As a result, several studies have attempted to classify subsets of patients with CVID on the basis of laboratory findings correlated with clinical features [9-14].

Memory B cells, characterized by cell-surface expression of CD27, rapidly generate immunoglobulins of all isotypes during secondary immune responses [15]. Class-switched $CD27^+$ IgM^- IgD^- memory B cells were first found to be absent in X-linked hyper-IgM syndrome [16]. Subsequently, a number of reports have described a reduction in $CD27^+$ memory B cells in peripheral blood from patients with CVID [12,17-21]. Warnatz et al [12] divided CVID patients into 2 groups: group I had less than 0.4% switched memory B cells in peripheral blood lymphocytes (PBL), while in group II switched memory B cells represented more than 0.4% of PBL. Group I patients were further subdivided into groups Ia and Ib according to the proportion of $CD21^-$ peripheral B cells. Comparison of clinical and laboratory findings in the different groups revealed that splenomegaly and autoimmune cytopenias were more frequent in group Ia. Piqueras et al [19] suggested a similar classification based on populations of memory B cells and demonstrated some clinical implications.

In this study, we examined the status of memory B cells in Iranian patients with CVID in relation to their laboratory and clinical characteristics.

Patients and Methods

Patients and Controls

The study included 29 patients with a diagnosis of CVID. Diagnosis of CVID was based on International Union of Immunological Societies criteria [22], including reduced levels of at least 2 serum immunoglobulins (IgG, IgA, and IgM) by 2 SD from normal mean values for the patient's age [23] and on typical medical history of recurrent bacterial infections [1,2]. Patients aged less than 2 years were excluded because of a possible diagnosis of transient hypogammaglobulinemia. To exclude other causes of hypogammaglobulinemia, patients with a B-cell count of less than 1% were subjected to Bruton's tyrosine kinase (BTK) mutation analysis and patients with a B-cell count of more than 1% were analyzed for activation-induced cytidine deaminase (AID) [24], *SH2D1A* [7], and CD40L [25] defects. Although patients with a low B-cell count may occasionally be misdiagnosed as having CVID when they carry a mutation in the *BTK* gene, this is not a common phenomenon [5]. All patients were treated by intravenous IgG replacement (400-500 mg/kg) every 3 to 4 weeks. Twenty age-matched healthy donors (13 male and 7 female; age range, 5-50 years; median age, 15 years) were also recruited as a control group.

All patients provided informed consent to inclusion in the

study. Informed consent was obtained from parents when the participant was younger than 18 years old.

Cell Preparation

A sample of 5 to 10 mL of blood was obtained from patients with CVID and age-matched healthy controls and treated with ethylenediaminetetraacetic acid. Blood samples from CVID patients were always obtained prior to intravenous immunoglobulin replacement. Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hypaque density gradient centrifugation and washed twice with phosphate-buffered saline. PBMCs were centrifuged through a layer of 100% heat-inactivated fetal calf serum (FCS; Gibco, Invitrogen Corporation, Carlsbad, USA) to reduce cell-bound IgG and resuspended in RPMI 1640 medium (Sigma, Deisenhofer, Germany) supplemented with 10% FCS.

Antibodies and Flow Cytometry

PBMCs (2.5×10^6 in 50 mL RPMI 1640 medium containing 10% FCS) were stained for 20 minutes at 4°C with 10 mL of a mixture of the following antibodies at optimal concentrations: phycoerythrin (PE)-Cy5 conjugated anti-CD19, fluorescein isothiocyanate (FITC)-conjugated anti-CD27, and PE-conjugated anti-IgD in the first tube; PE-Cy5-conjugated anti-CD19; FITC-conjugated anti-CD27, and PE-conjugated anti-IgM in the second tube; and PE-Cy5-conjugated anti-CD19 and FITC-conjugated anti-CD21 in the third tube. All antibodies were from Dako (Glostrup, Denmark). Two-color and 3-color data acquisition was performed with a FACSCalibur flow cytometer (Becton Dickinson, Mountain View, USA). Data analysis was performed with CellQuest software (Becton Dickinson) by forward scatter versus side scatter gating on viable PBLs in combination with gating on $CD19^+$ cells. Four thousand $CD19^+$ cells were acquired and the percentages of naive, IgM-memory, and class switched (IgM^-IgD^-) memory B cells (Figure 1) were calculated [12].

Statistical Analysis

Statistical comparisons of quantitative data were made using the unpaired Student *t* test. When the data did not fulfill the criteria for applying parametric tests, non-parametric statistics were used (Mann-Whitney *U* Test, Spearman correlation coefficient). Nominal data were evaluated by Fisher exact test. Differences between groups were considered significant at $P < .05$. The data were analyzed using the statistical software package SPSS version 11.5 (SPSS Inc, Chicago, USA).

Results

Patient Characteristics

Twenty-nine patients with CVID (18 male and 11 female) were included in the study (age range, 2.5-56 years; median, 14 years). Serum IgG, IgA, and IgM concentrations were reduced by more than 2 SD in all patients compared with the mean values for healthy individuals of the same age. Table 1 shows the general characteristics, serum immunoglobulin concentrations, and distributions of lymphocyte subtypes in the patients with CVID.

Memory B Cells in Patients with CVID

The patients were classified into 3 groups according to

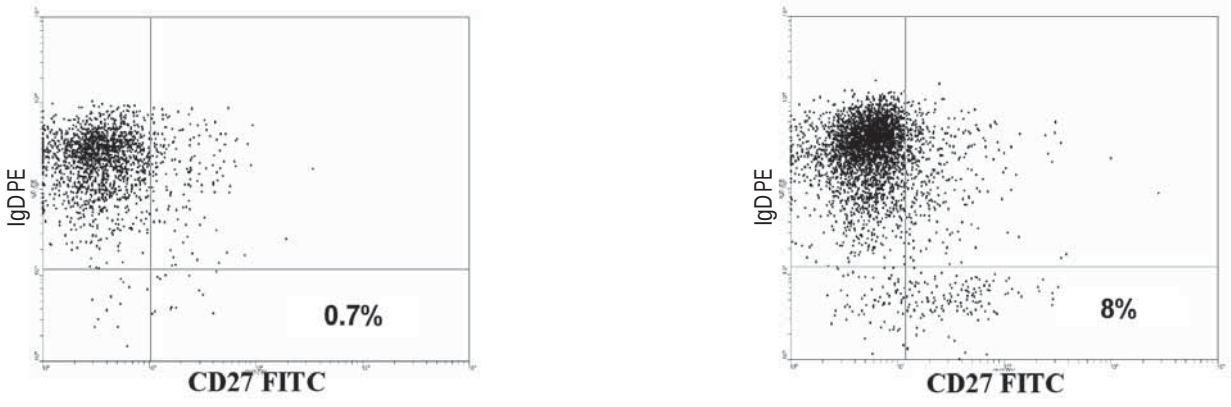

Figure 1. Peripheral B cells in 2 patients with common variable immunodeficiency. Representative histograms of group I (left) and group II (right) patients are shown. Four thousand $CD19^+$ B cells were scanned for each patient. The group I patient had switched memory B cells accounting for 0.7% of peripheral B cells. The example from group II had switched memory B cells accounting for 8% of peripheral B cells.
Ig indicates immunoglobulin; PE, phycoerythrin; FITC, fluorescein isothiocyanate.

Table 1. Characteristics of Patients With Common Variable Immunodeficiency*

Number	Sex	Age, y	IgG, mg/dL	IgM, mg/dL	IgA, mg/dL	CD3, %	CD4, %	CD8, %	CD19, %	Classification
1	Male	12.5	240	46	60	63	29	23	11.5	II
2	Female	16.5	50	10	2	82	36	40	2.7	Ia
3	Male	8.5	140	10	5	77	31	25	11.8	Ib
4	Female	2.5	16	27	7	80	50	45	5.15	Ia
5	Male	15	360	42	5	63	7	50	6.9	Ib
6	Male	27	40	5	1	84	42	46	3.6	Ib
7	Male	18	10	10	1	65	28	30	16.15	Ib
8	Female	4	500	45	5	72	17	51	18.5	II
9	Female	6	200	13	10	61	40	13	10.52	Ia
10	Male	48	125	10	2	77	25	55	8.9	Ib
11	Male	14	50	12	5	68	21	44	16.07	Ia
12	Male	8	100	20	10	65	44	32	5.9	Ib
13	Male	12	470	50	37	69	29	39	9.1	Ib
14	Female	16.5	460	60	76	87	38	35	15.5	II
15	Female	6	250	20	10	38	14	28	7.87	II
16	Male	35	200	70	5	54	31	20	7.57	II
17	Female	20	500	46	20	90	12	78	2.15	Ia
18	Female	11	114	30	52	66	35	31	20.1	Ib
19	Male	47	75	11	3	71	24	46	5.12	Ib
20	Male	12	10	24	2	99	50	35	5.8	Ib
21	Female	56	270	20	10	86	23	56	11.03	II
22	Female	18.5	480	32	10	81	39	37	4.7	II
23	Male	7	380	48	5	59	17	42	2.5	Ib
24	Male	12.5	29	10	10	65	32	34	1.1	Ia
25	Male	6.5	10	36	22	62	27	35	14.8	Ib
26	Female	22	342	20	10	42	31	16	10	Ib
27	Male	26	80	10	20	76	38	31	10.75	Ib
28	Male	32	185	80	5	75	19	57	8.55	II
29	Male	14	240	30	28	65	31	34	12.5	II

*Ig indicates immunoglobulin

the percentages of memory B cells and switched memory B cells [12]. Compared with 20 healthy control subjects, the patients with CVID had lower percentages of both memory B cells and class-switched memory B cells (Figure 2). In all healthy donors, more than 0.4% (mean ± SD, 1.2% ± 0.5%) of PBLs belonged to the $CD27^+IgM^-IgD^-$ cell population. In contrast, the percentage of switched memory B cells in 20 out of 29 patients (69%) was less than 0.4% (mean, 0.17% ± 0.01%); those patients were classified as group I. A less marked reduction in the percentage of class-switched memory B cells was found in 9 patients (31%) designated as group II (mean ± SD, 0.6% ± 0.3%). We further subdivided group I patients into those with an increased proportion of $CD21^-$ peripheral B cells (>20%, group Ia) and those with

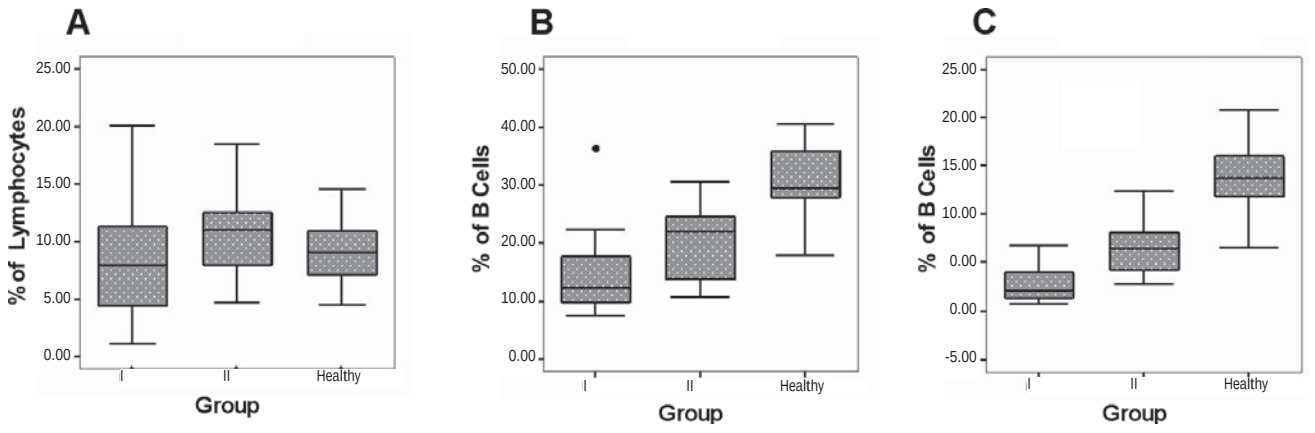

Figure 2. The relative frequency of each subset within the B-cell compartment is shown as a box plot for mature (A), memory (B), and switched memory B-cells (C). Boxes represent values between the 25th and 75th percentiles. The horizontal line corresponds to the median.

normal percentages of $CD21^-$ B cells (<20%, group Ib). Six patients belonged to group Ia, 14 to group Ib, and 9 to group II (Tables 2 and 3).

The percentage of $CD19^+$ B cells was comparable in groups Ia (mean, 6.3% ± 5.8%), Ib (mean, 9.5% ± 5%), and II (mean, 11% ± 4.2%) and did not differ significantly from that seen in healthy donors (mean, 9.1% ± 2.7%) (Table 3).

Immunoglobulin Production in Patients with CVID

We examined serum immunoglobulin concentrations (IgG, IgM, and IgA) at the time of diagnosis and before immunoglobulin replacement. The concentration of IgG was significantly lower in groups Ia (median, 50 mg/dL; $P = .05$) and Ib (median, 107 mg/dL; $P = .01$) than in group II (median, 250 mg/dL). Likewise, serum concentrations of IgM were lower in groups Ia (median, 12.5 mg/dL; $P = .01$) and Ib (median, 20 mg/dL; $P = .01$) than group II (median, 45 mg/dL; $P = .01$). In contrast, median serum IgA concentrations were similar in all 3 groups (Table 2).

Clinical Findings in Subsets of CVID Patients

Tabla 2. Clinical Characteristics of Patients with Common Variable Immunodeficiency in Different Groups*

	Group		
	Ia (n = 6)	Ib (n = 14)	II (n = 9)
Male/Female	2/4	12/2	4/5
Current age, y	13.2 (2.5-20)	13.5 (6.5-48)	16.5 (4-56)
Age at onset, y	3 (1.5-6)	1.7 (0.5-35)	7 (0.5-46)
Age at diagnosis, y	11 (3-13)	8.5 (2.5-40)	10 (2.5-46)
Diagnostic delay, y	7 (0.5-9.5)	4.7 (0.5-39)	3 (0.5-28)
Median IgG, mg/dL	50 (16-500)	107 (10-469)	250 (185-500)
Median IgM, mg/dL	12.5 (10-46)	20 (5-50)	45 (20-80)
Median IgA, mg/dL	8.5 (2-20)	5 (1-52)	10 (5-76)
Splenomegaly	4 (66%)	5 (35%)	4 (44%)
Autoimmunity	4 (66%)	3 (21%)	1 (11%)
Bronchiectasis	2 (33%)	9 (64%)†	0
Lymphoid proliferation	1 (17%)	0	1 (7.1%)

*Data are shown as the number (%) for discrete variables and median (interquartile range) for continuous variables.
†$P = .002$ compared to group II

Tabla 3. Percentage of B Lymphocyte Subpopulations and Serum Immunoglobulin Concentrations in Patients With Common Variable Immunodeficiency*

	Group				
	CVID (n=29)	Ia (n=6)	Ib (n=14)	II (n=9)	**Control (n=20)**
$CD19^+$, %	9.2 ± 5.8	6.3 ± 5.8	9.5 ± 5	11 ± 4.2	9.1 ± 2.7
$CD27^+$, % of $CD19^+$	16.5 ± 7.4†	15.5 ± 4.3†	14.5 ± 8†	21 ± 7.3	31 ± 6.5
IgD^+ $CD27^-$, % of PBL	7.6 ± 4.5	5.1 ± 4.9	8.5 ± 4.5	8.5 ± 4.0	6.0 ± 1.8
IgD^+ $CD27^+$, % of PBL	1.0 ± 0.6†	0.7 ± 0.6†	1.0 ± 0.4†	1.5 ± 0.6	1.4 ± 0.5
IgD^- $CD27^+$, % of PBL	0.3 ± 0.2†	0.1 ± 0.05†	0.2 ± 0.06†	0.6 ± 0.3†	1.2 ± 0.5
$CD21^-$, % of $CD19^+$	16.5 ± 19.5†	48.5 ± 22.5†	9.0 ± 3.5†	7.2 ± 4.6	5.5 ± 2.0

*Data are shown as means ± SD. CVID indicates common variable immunodeficiency; PBL, peripheral blood lymphocytes.
†Statistically significant differences from the control group ($P < .05$)

We found no significant differences in the patients' age between groups Ia, Ib, and II. Comparison of memory B cells in groups I and II by age revealed a statistically significant correlation between higher percentages of memory B cells and increasing age in group I ($\rho = 0.532$, $P = .01$) but not in group II ($\rho = -0.27$, $P = .47$). The clinical characteristics of patients belonging to different subclasses are shown in Table 2.

Autoimmune diseases were found in 4 patients in group Ia (Evans syndrome in 2 patients, neutropenia in 1, and autoimmune hepatitis in 1), 3 patients in group Ib (Evans syndrome in 1 patient, immune thrombocytopenic purpura in 1 patient, and myasthenia gravis/hypothyroidism in 1 patient), and 1 patient (psoriasis) in group II. Splenomegaly was seen in 66% of group Ia patients, 35% of group Ib, and 44% of group II. Clustering of these clinical findings was not statistically significant in the different groups.

Chest radiography and high-resolution computed tomography (HRCT) scans were performed in all patients to assess lung damage. The prevalence of bronchiectasis was 33% in group Ia and 64% in group Ib, while no patients in group II developed bronchiectasis.

Discussion

CVID comprises a heterogeneous group of primary antibody deficiencies characterized by hypogammaglobulinemia and recurrent bacterial infections. Previous attempts have been made to understand and classify CVID on the basis of in vitro B cell immunoglobulin production and analysis of T-cell function after stimulation. Although the functional classification proposed by Bryant et al [11] is of use in the identification of disease subtypes, it is not generally accepted, and it is not often applied because of the difficulty of synthesizing immunoglobulins in vitro and the lack of correlation with clinical features.

Since the demonstration of CD27 as a reliable marker for identification of functional memory B cells [15], several groups have examined memory B cell compartments in patients with CVID [12-14,19,26,27]. In human peripheral blood, $CD27^+$ memory B lymphocytes can be subdivided into 2 distinct subsets: IgD^-CD27^+, which synthesizes IgG, IgM, or IgA (switched cells), and IgD^+CD27^+, which predominantly produces IgM (nonswitched cells) [28].

Brouet et al [17] and Jacquot et al [18] found decreased $CD27^+$ memory cells in 70% and 58% of studied CVID patients, respectively. Agematsu et al [16] found that IgD^- $CD27^+$ memory B cells were markedly reduced or absent in 24 studied subjects with X-Linked hyper-IgM syndrome. However, neither group assessed the correlations between their data and the extended clinical phenotype.

A new classification of CVID based on memory B cell pool was proposed by both Warnatz et al [12] and Piqueras et al [19]. Warnatz et al analyzed memory B cell populations in PBL from CVID patients by flow cytometry. Patients with less than 0.4% class-switched memory B cells were termed group I and those with greater than 0.4% class-switched memory B cells among their PBLs were termed group II. Group I patients were further subdivided into those with an increased proportion of $CD21^-$ peripheral B cells (> 20%, group Ia) and patients with normal percentages of $CD21^-$ B cells (< 20%, group Ib). Significant clustering of CVID patients with splenomegaly and autoimmune cytopenias was found in group Ia. Piqueras et al proposed a classification of B cells based on the coexpression of IgD and CD27. This classification also correlates with some

clinical aspects of CVID.

In this study, 29 Iranian CVID patients were classified according to the status of memory B cells [12]. All patients were found to have lower percentages of memory B cells compared to the control group, while 20 patients (69%) were assigned class I. Similar results have been reported in previous studies [12,19]. Autoimmune diseases were found in all 3 groups but the highest proportion was found in group Ia. Our results are similar to those reported by Warnatz et al [12], who found autoimmunity to be more concentrated in group I patients. Splenomegaly was seen in all groups with no significant differences observed between them; this is in contrast to the findings of Warnatz et al [12], who reported that all of the patients in group Ia had splenomegaly, whereas a lower proportion of patients was affected in the other groups.

Bronchiectasis, confirmed by HRCT, was seen in 37% of our patients. All of the patients with bronchiectasis belonged to group I, highlighting the importance of memory B cell function for protection against chronic lung damage in CVID patients. The patients in group I had lower levels of IgG and IgM than those in group II. However, this difference would have had little effect on bronchiectasis predisposition, since bronchiectasis develops despite adequate immunoglobulin replacement therapy in CVID patients [29]. This is supported by the results of a recent study by Alachkar et al [27] indicating that a reduction in the percentage of class-switched memory B cells but not serum immunoglobulin levels is associated with a significantly higher prevalence of bronchiectasis.

Recent studies have evaluated the in vivo antibody response in relation to memory B cells. Ko et al [21] showed that CVID patients with decreased percentages of switched memory B cells have lower levels of serum IgG and less-effective antibody responses to pneumococcal vaccine. Although we did not evaluate the response to pneumococcal vaccine in all patients, an abnormal antibody response to polysaccharide antigens may explain the exclusive development of bronchiectasis in group I patients. Carsetti et al [8] reported that IgM memory B cells and antipneumococcal IgM antibodies protect patients with CVID from bacterial pneumonia and resulting bronchiectasis. Those results indicate that residual B-cell function, resulting in the differentiation of IgM memory B cells and the production of detectable levels of antipneumococcal IgM, explains the rarity of pulmonary infection in some patients with severe hypogammaglobulinemia.

In our study, there was a statistically significant correlation between increasing age and an increased proportion of memory B cells in group I, an observation which is in agreement with the finding of increasing numbers of memory B cells with increasing age reported in healthy individuals [30].

Because the development of memory B cells is essentially linked to the formation of germinal centers in secondary lymphoid organs [31] the finding of a significantly reduced switched memory B-cell compartment in CVID type I strongly supports the hypothesis that germinal center reactions are disturbed in this disease [32].

Our finding that bronchiectasis is more prevalent in patients with decreased switched memory B cells indicates a clinical association for this subset of CVID. Also, the observation of more patients with autoimmune disease in group I suggests that patients lacking switched memory B cells are more likely to produce autoantibodies.

Shortly after its introduction, subclassification of CVID patients based on memory B cells has proved its efficacy in revealing the pathogenesis of CVID. It has recently been shown that mutations in *ICOS* and *TACI* can cause a phenotype indistinguishable from CVID [33,34]. Both mutations result in diminished memory B cells and even a greater reduction in switched memory B cells in the peripheral blood.

In conclusion, we have shown that subclassification of CVID patients according to the proportion of B cell switching has meaningful clinical correlations: patients with decreased percentages of switched memory B cells have lower levels of IgG/IgM and higher rates of autoimmune disease and bronchiectasis. Thus, assessment of switched memory B cells could predict clinical prognosis in CVID patients.

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Manuscript received December 21, 2006; accepted for publication March 16, 2007.

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