Presence of Idiopathic Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia in the Patients with Common Variable Immunodeficiency

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ABSTRACT

Common Variable Immunodeficiency (CVID) is a heterogeneous group of disorders characterized by hypogammaglobulinemia and an increased susceptibility to recurrent infections as well as autoimmunity and malignancies. Idiopathic Thrombocytopenic Purpura (ITP) and Autoimmune Hemolytic Anemia (AIHA) are two autoimmune disorders which may be seen in association with CVID.

Among 85 CVID patients, seven cases had ITP and/or AIHA (8%). Four of these patients had one or more episodes of ITP, one patient had AIHA, and two patients had both ITP and AIHA (Evans syndrome).

Almost all patients experienced chronic and recurrent infections mostly in respiratory and gastrointestinal systems during the course of the disease. Among the seven patients, five presented their underlying disease with recurrent respiratory and/or gastrointestinal tract infections, while in two remaining patients, CVID was presented with ITP. Three patients died until now; two because of hepatic failure and one due to pulmonary hemorrhage.

As CVID is prone to autoimmune disorders, it should be considered as a differential diagnosis of adult-onset ITP and possibly in children. Chronic and recurrent ITP, especially in the presence of propensity to respiratory and gastrointestinal infections mandate the evaluation for an underlying immune dysregulation such as CVID.

Keywords: Autoimmune Hemolytic Anemia; Common Variable Immunodeficiency; Idiopathic Thrombocytopenic Purpura

INTRODUCTION

Common Variable Immunodeficiency (CVID) is a heterogeneous group of disorders, characterized by
hypogammaglobulinemia, defective specific antibody production and an increased susceptibility to chronic and recurrent infections, mostly upper and lower respiratory and gastrointestinal tracts.\(^1\)\(^-\)\(^4\) CVID is the most prevalent symptomatic primary immunodeficiency disease with an estimated prevalence of one per 10,000 to one per 50,000, depending on the country and the type of the study.\(^5\)\(^-\)\(^8\) The clinical spectrum of CVID manifestations is broad, and it may be presented at any age, but the peak of occurrence appears in childhood and early adulthood.\(^1\)\(^,\)\(^2\) Several defects in B cell differentiation, as well as abnormalities of T cells and dendritic cells have been reported in some studies.\(^9\)\(^-\)\(^13\)

It is noteworthy that patients with CVID have an increased incidence of autoimmune disorders and cancers (14-16). Approximately, 20-25% of patients with CVID develop autoimmune disorders in which idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) are the most frequent. There are few documented studies on the prevalence of ITP and/or AIHA in patients with CVID.\(^17\)\(^-\)\(^21\) One large study of 326 patients with CVID, demonstrated that 35 (11%) patients had a history of ITP and/or AIHA.\(^19\) ITP may be the first manifestation and precede the diagnosis of CVID.\(^20\) The pathogenesis of autoimmune hematologic complications among patients with CVID is not well defined.

To describe the clinical features and outcome of ITP and/or AIHA among patients with CVID, we report clinical and laboratory characteristics in 7 CVID patients who manifested autoimmune hematologic disorders.

**PATIENTS AND METHODS**

**Patients**

Children Medical Center Hospital is the referral center for primary immunodeficiency disorders in Iran. All patients with CVID who were diagnosed and treated during a 27 year period (1980-2007) in this hospital were investigated in this study.

The diagnosis of patients was based on the standard criteria, suggested by the European Society for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency (PAGID).\(^22\) Diagnosis of CVID was based on hypogammaglobulinemia and variable number of B cells (>2%) and exclusion of other well known single gene defects.\(^23\)\(^-\)\(^27\)

ITP was defined according to the criteria suggested by the American Society of Hematology Guideline.\(^28\) The clinical manifestations of thrombocytopenia included petechiae and bruising. The diagnosis of active autoimmune hemolytic anemia was defined as a decrease of at least 2 g/dL in hemoglobin serum levels, with features of hemolysis and a positive direct antiglobulin test after the exclusion of other causes of acquired or hereditary hemolytic anemia.

**Methods**

A two-page questionnaire was designed to collect all necessary information from studied patients, including: past medical histories, the onset of CVID, onset and episodes of ITP and/or AIHA, other associated complications of CVID and the required treatments.

In 5 out of 7 patients, the results of switching of B-cell and quantification of peripheral blood memory B cells were obtained, which has previously been reported.\(^13\) Briefly, the percentages of switched memory B cells (CD27+IgM-IgD- cells/peripheral B lymphocytes) in these patients were compared with healthy control subjects using flow cytometry (FACScan; Becton Dickinson, Mountain View, CA). Patients were subdivided into groups I and II based on percentages of switched memory B cells (greater or less than 0.4% respectively).

**RESULTS**

In this retrospective study, the hospital records of 85 patients with CVID (42 males and 43 females), with age range of 3 to 48 years, were reviewed. Among 85 patients, 7 sporadic cases (5 males and 2 females) had the history of ITP and/or AIHA (8%).

Four of these patients had one or more episodes of ITP (P1, P2, P4, and P6), one patient (P3) had AIHA, and 2 patients (P5, P7) had both ITP and AIHA (Evans syndrome). In these 7 patients, the median age at the time of diagnosis of CVID and ITP were 8 (range: 2-23) and 11 (range: 2-12) years, respectively. All episodes of ITP and/or AIHA occurred before the age of fifteen years (Table 1). Immunological data of the patients are presented in the table 2. All patients had decreased serum levels of IgG, IgM and IgA. While two patients had the ratio of CD4/CD8 more than one, five patients had reverse ration of CD4/CD8.
Autoimmune Hematological Diseases in CVID

Table 1. Characteristics of CVID patients with ITP and/or AIHA

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Status</th>
<th>Age at diagnosis of CVID (years)</th>
<th>Age at diagnosis of ITP and/or AIHA (years)</th>
<th>First clinical manifestations</th>
<th>Other complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>Male</td>
<td>Alive</td>
<td>2</td>
<td>5</td>
<td>Diarrhea</td>
<td>-</td>
</tr>
<tr>
<td>P2</td>
<td>Male</td>
<td>Dead</td>
<td>3.5</td>
<td>11</td>
<td>Otitis media</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>P3</td>
<td>Female</td>
<td>Alive</td>
<td>13</td>
<td>12</td>
<td>Otitis media</td>
<td>RA</td>
</tr>
<tr>
<td>P4</td>
<td>Male</td>
<td>Alive</td>
<td>8</td>
<td>9</td>
<td>Pneumonia</td>
<td>-</td>
</tr>
<tr>
<td>P5*</td>
<td>Female</td>
<td>Dead</td>
<td>11</td>
<td>12</td>
<td>Sinusitis</td>
<td>MALT</td>
</tr>
<tr>
<td>P6</td>
<td>Male</td>
<td>Dead</td>
<td>8.5</td>
<td>11</td>
<td>ITP</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>P7*</td>
<td>Male</td>
<td>Alive</td>
<td>6</td>
<td>2</td>
<td>ITP</td>
<td>IBD</td>
</tr>
</tbody>
</table>

RA: Rheumatoid Arthritis, MALT: Mucosal Associated Lymphoid Tumor; IBD: Inflammatory Bowel Disease
* Patients with both ITP and AIHA (Evans syndrome)

Five out of the above seven patients expressed the underlying disease with recurrent respiratory and/or gastrointestinal tract infections, whereas two patients (P3 and P7) developed ITP prior to CVID diagnosis (Table 1). Almost, all 7 patients experienced chronic and recurrent infections mostly of respiratory and gastrointestinal systems during the course of the disease (Table 3). Moreover 4 patients had other autoimmune complications, including neutropenia (P2 and P6), juvenile rheumatoid arthritis (P3) and inflammatory bowel disease (P7) in addition to hematologic autoimmune diseases.

Six out of 7 patients were tested for the presence of circulating antiplatelet antibodies by a standard indirect immunofluorescence method, and a positive result was found in 3.

In order to understand the relationship between autoantibody production and development of autoimmune hematologic disorders, the percentage of switched memory B cells was determined. Accordingly, five out of 7 patients had low percentages of switched memory B cells (CD27+IgM-IgD- cells/peripheral B lymphocytes) (less than 0.4 %) (p<0.05) and were classified as group I.

All of these five patients were found to lack the switched memory B cells and whereas they had an increased proportion of immature B cells. The remaining two patients were not available at the time of measuring switched memory B cells.

CVID and Evans syndrome on P5 who has been previously described,29 were diagnosed at the age of 12 and 13 years respectively. The patient presented chronic cough and wheezing resistant to therapy. High resolution computerized tomography (HRCT) scan in this patient was performed and it revealed diffuse alveolar infiltration with interstitial fibrosis. Immunohistochemical study of obtained specimen from open lung biopsy was compatible with mucosal associated lymphoid tissue (MALT) lymphoma.29 As she had both Evans and MALT Lymphoma and corticosteroids failed to increase the platelets count, she was administered anti-CD20 (Rituximab) therapy. The patient showed an initial response to anti-CD20 and her platelet count returned to normal. However six months after anti-CD20 therapy; she experienced another relapse of severe ITP and finally passed away due to pulmonary hemorrhage.

Table 2. Immunological and hematological studies of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>IgG (mg/dl)</th>
<th>IgM (mg/dl)</th>
<th>IgA (mg/dl)</th>
<th>Hb (gr/dl)</th>
<th>Platelet (cells/mm³)</th>
<th>WBC (cells/mm³)</th>
<th>Lymphocyte (%)</th>
<th>CD19 (%)</th>
<th>CD3 (%)</th>
<th>CD4 (%)</th>
<th>CD8 (%)</th>
<th>CD4/CD8</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>380</td>
<td>48</td>
<td>10.2</td>
<td>76700</td>
<td>8400</td>
<td>43</td>
<td>4.0</td>
<td>54.0</td>
<td>12.0</td>
<td>38.0</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>0</td>
<td>73</td>
<td>9.0</td>
<td>108000</td>
<td>4800</td>
<td>40</td>
<td>10.0</td>
<td>55.0</td>
<td>20.0</td>
<td>33.0</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>P3</td>
<td>500</td>
<td>10</td>
<td>12.0</td>
<td>95000</td>
<td>7000</td>
<td>60</td>
<td>3.5</td>
<td>90.1</td>
<td>12.9</td>
<td>78.6</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>P4</td>
<td>770</td>
<td>10</td>
<td>11.2</td>
<td>85000</td>
<td>3900</td>
<td>45</td>
<td>7.5</td>
<td>80.9</td>
<td>43.6</td>
<td>34.6</td>
<td>1.26</td>
<td></td>
</tr>
<tr>
<td>P5</td>
<td>170</td>
<td>20</td>
<td>7.2</td>
<td>47000</td>
<td>4420</td>
<td>23</td>
<td>5.9</td>
<td>82.6</td>
<td>32.5</td>
<td>44.6</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td>P6</td>
<td>320</td>
<td>7.5</td>
<td>10.4</td>
<td>48000</td>
<td>3800</td>
<td>48</td>
<td>5.7</td>
<td>78.2</td>
<td>55.2</td>
<td>20.0</td>
<td>2.76</td>
<td></td>
</tr>
<tr>
<td>P7</td>
<td>160</td>
<td>40</td>
<td>8.1</td>
<td>17000</td>
<td>5100</td>
<td>35</td>
<td>3.9</td>
<td>88.3</td>
<td>31.3</td>
<td>55.5</td>
<td>0.57</td>
<td></td>
</tr>
</tbody>
</table>
Hematological disorders in patients P1 and P3 went into remission after corticosteroids therapy. Patient P3 normalized platelet counts after monotherapy with corticosteroids; however, this patient experienced an ITP relapse for which no further treatment was required. Among the rest of these patients, P3 and P7 experienced ITP before diagnosis of CVID in whom, the number of platelets was increased spontaneously without receiving any treatment. P2 and P4 who regularly received courses of IVIG therapy increased their platelet count when the IVIG dosage was increased. The median follow-up time for these patients was 7 years (range: 4-15); three patients died until now. The causes of death were hepatic failure in P2 and P3; and pulmonary hemorrhage in P5.

**DISCUSSION**

CVID patients are susceptible to recurrent infections and may present with autoimmune disorders in a frequency approximately 20-25%. The most common hematological elements involved in autoimmune phenomena are platelets (idiopathic thrombocytopenic purpura), red blood cells (autoimmune hemolytic anemia), and occasionally neutrophils.

Autoimmunity is a common complication in primary immunodeficiency diseases, in which B cells are present, but their function is impaired. Two most common autoimmune conditions in CVID patients are ITP and AIHA. In this study, 8% of the patients appeared with either of the condition or a combination of the two, as has also been shown in previous studies. In the general population, ITP occurs in 1.0-12.5 per 100,000 per year, affecting children or adults.

In contrast to classical ITP, where females comprise the bigger proportion of patients, in our series 71% of the CVID patients with ITP, were male. This finding is in concordance with previous publications reporting which showed a female/male ratio of less than primary ITP. In a study performed in France, 60% of ITP patients were male. Also in a survey of 326 patients with CVID, in which 35 (11%) had a history of ITP and/or AIHA, the female/male ratio was 1.18, which is at any rate less than what is predicted in patients affected with primary ITP. These results suggest that immunologic abnormalities found in CVID are the major single risk factor for developing ITP.

As previously shown, ITP may be the preceding finding prior to infectious complications of CVID. Accordingly, two patients in our study developed ITP and/or AIHA before the patients were diagnosed as CVID. Thus, CVID needs to be included in the differential diagnoses of adult-onset ITP and possibly for children. Collectively, serum immunoglobulins should be measured as the patient is treated for ITP, even in the absence of severe infections.

Although the autoimmune nature of CVID among adults and children is not well understood, the production of auto-antibodies may be one of the consequences of immune dysregulation. Paradoxically, these patients are unable to produce an antibody response to infectious agents, but retain the ability to produce autoantibodies against their erythrocytes, platelets, and granulocytes. This has been attributed to defects in antibody affinity maturation. It was demonstrated that CVID patients lacking switched memory B cells are more susceptible to autoimmunity. This is in concordance with what we stated above about the 5 patients with low class switched memory B cells and ITP.

Treatment options for ITP include corticosteroids, IVIG, anti-D, splenectomy and anti-CD20 (Rituximab). Steroids are usually the first-line of treatment. However, immunosuppression should be
induced cautiously because of higher risk of infections.2
Administration of IVIG could increase the platelet counts in children with acute or chronic ITP.40 A platelet count of more than 20000/mm³ can be achieved with low-dose IVIG in most children with acute ITP, however for patients with very low platelet counts, higher doses would be more effective.41
Four of our patients improved without any specific therapy other than regular IVIG; three of them required corticosteroids and higher doses of IVIG. There are reports which support the idea that intensive therapeutic interventions have no impact on the outcome of chronic ITP.42-45 This approach avoids side effects and reduces costs.
None of our patients underwent splenectomy. In 2 large cohorts studies2,34 including a total of 498 CVID patients, just 30 patients underwent splenectomy, which was associated with serious complications such as pneumococcemia and severe postoperative infections. Splenectomy should be reserved as a last choice for refractory cases.
Rituximab is a genetically engineered, humanized, mouse monoclonal antibody directed against the CD20 and has been studied for treatment of various antibody mediated disorders including refractory ITP and AIHA.46-49
There are few reports of CVID patients with ITP and/or AIHA who benefited of rituximab.39,50,51 The only one case with persistent ITP and AIHA who received rituximab, showed partial platelet count increase, which unfortunately relapsed after six months.
To sum up, ITP in children is usually a benign disease remitting within weeks to months. Chronic and recurrent ITP, especially in the presence of propensity to respiratory and gastrointestinal infections mandate the evaluation for an underlying immune dysregulation such as CVID.

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