Autoimmune Thrombocytopenic Purpura and Common Variable Immunodeficiency

Analysis of 21 Cases and Review of the Literature

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Abstract: To describe the main characteristics and outcome of autoimmune thrombocytopenic purpura (AITP) in patients with common variable immunodeficiency (CVID), we analyzed data from 21 patients and reviewed additional cases from the literature. To be included in this study, patients had to have CVID and a previous history of AITP with a platelet count $\leq 50 \times 10^9$/L at onset. A complete response to treatment was defined by a platelet count $\geq 150 \times 10^9$/L, and a partial response by a platelet count $>50 \times 10^9$/L with an increase of at least twofold the initial level. The median platelet count at AITP diagnosis was 20×10^9/L (range, $2–50 \times 10^9$/L). The median age at AITP diagnosis was 23 years (range, 1–51 yr), whereas the median age at CVID diagnosis was 27 years (range, 10–74 yr). CVID was diagnosed before the onset of AITP in only 4 patients (19%), 3 of whom were being treated with intravenous immunoglobulin (IVIg) replacement therapy. CVID was diagnosed more than 6 months after AITP in 13 cases (62%), and the 2 conditions were diagnosed concomitantly in 4 cases. Eleven patients (52%) had at least 1 autoimmune manifestation other than AITP, among which autoimmune hemolytic anemia (7 cases) and autoimmune neutropenia (5 cases) were preeminent.

Seventeen of the 21 patients (80%) received at least 1 treatment for AITP; 13 patients received corticosteroids alone and 7 (54%) achieved at least a partial response; 8 patients received IVIg at 1–2 g/kg alone or in combination with steroids, leading to a short-term response rate of 50%. Four patients underwent a splenectomy (2 complete responses, 2 failures); 2 additional splenectomies were performed for associated autoimmune hemolytic anemia. With a mean follow-up of 5.6 years after the surgical procedure, none of the 6 splenectomized patients had a life-threatening infection. With a median follow-up after AITP onset of 12 years, 13/21 patients (62%) were in treatment-free remission (7 complete responses, 6 partial responses), 7 patients (23%) were in remission while on prednisone ≤ 20 mg/day with or without azathioprine, and only 1 patient still had a platelet count $<50 \times 10^9$/L. Five patients had died at the time of the analysis; none of the deaths was related to a hemorrhage. Severe infections including 3 fatal bacterial infections and 2 opportunistic infections occurred in 6 patients during or after treatment of AITP. In conclusion, AITP, alone or in combination with autoimmune hemolytic anemia (Evans syndrome) and/or autoimmune neutropenia, is frequent in patients with CVID, and is not prevented by IVIg substitutive therapy. Since AITP frequently precedes the diagnosis of CVID, testing for immunoglobulin levels should be performed in every patient diagnosed with AITP. Steroids and splenectomy seem to have the same efficacy as in idiopathic AITP, but the increased risk of severe infections must be taken into consideration.

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Abbreviations: AITP = autoimmune thrombocytopenic purpura, CVID = common variable immunodeficiency, IVIg = intravenous immunoglobulin.

INTRODUCTION

Common variable immunodeficiency (CVID) is a heterogeneous syndrome with an unknown etiology, characterized by hypogammaglobulinemia and recurrent bacterial infections[25]. A marked decrease in serum IgG associated with a significant reduction of serum IgM and/or IgA levels is the hallmark of the disease. Besides recurrent infections, patients with CVID also have an increased risk of autoimmune disease and malignancy[23,25], indicating that CVID is a disease of abnormal immune regulation as well as immunodeficiency[24]. Approximately 20%–22% of patients with CVID develop autoimmune disease, among which

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autoimmune thrombocytopenic purpura (AITP) and autoimmune hemolytic anemia are preeminent[3,4,24]. AITP is an acquired bleeding disorder in which antiplatelet autoantibodies bind to antigens on the surface of platelets, resulting in their accelerated destruction[7,8]. Whereas in children, AITP is usually triggered by a viral infection and its course is often acute and benign, AITP in adults is chronic in more than two-thirds of the cases, and its management often requires splenectomy and/or the use of immunosuppressive therapies (that is, corticosteroids, cytotoxic agents)[7].

To describe better the features and outcome of AITP occurring in patients with CVID as well as the consequences of the treatment of AITP on CVID course, we report here the characteristics of 21 patients diagnosed with these 2 conditions and discuss data from additional, previously reported cases.

PATIENTS AND METHODS

Study Design

The study was a multicenter retrospective study. All patients included were seen in the 15 years from 1986 to 2001 in 1 of the 5 participating centers. All cases of AITP from a cohort of 105 adults (aged 16 yr and older) with a definite diagnosis of CVID were retrospectively reviewed.

Inclusion Criteria

AITP was defined according to the criteria set forth in the American Society of Hematology Guidelines[9]. Only patients with a platelet count $\leq 50 \times 10^9$/L on at least 2 separate occasions over a 2-week period, with a normal bone marrow analysis, were included. Patients with mild splenomegaly in the setting of nonmalignant lymphoid hyperplasia were not excluded unless they had a proven lymphoma, chronic liver disease with portal hypertension, and/or chronic hepatitis C, or if they were human immunodeficiency virus (HIV)-positive.

The diagnosis of CVID was assessed by a level of gammaglobulin on serum protein electrophoresis of $\leq$500 mg/dL, on at least 2 separate occasions over 1 month, with a decrease below the normal level of at least 2 of the 3 major serum immunoglobulins (that is, IgG, IgA, and IgM) assessed by a quantitative measurement of serum immunoglobulin concentrations (see Table 1 for normal values). Patients with secondary hypogammaglobulinemia (long-term steroid therapy, lymphoma, protein-losing enteropathy)[3] with isolated primary IgA deficiency or X-linked agammaglobulinemia were excluded from the study.

Clinical and laboratory data for each patient were collected and analyzed by the same investigator (VC) using a standardized form.

In patients whose AITP required specific management, the response to therapy and the outcome were defined as followed: *failure* if the platelet count remained $<50 \times 10^9$/L; *partial response* if the platelet count increased at least twofold the initial value to a level $>50 \times 10^9$/L; and *complete response* if the platelet count rose above 150×10^9/L. Acute AITP was defined by a treatment-free complete remission of thrombocytopenia within 6 months of AITP onset.

For the literature review, only cases reported from 1980 to 2002, available on the PubMed (National Library of Medicine, Bethesda, MD) database, and fulfilling the above inclusion criteria were considered. The search terms used to perform the PubMed search were ''immune thrombocytopenic purpura,'' ''autoimmune hemolytic anemia,'' and ''autoimmune diseases'' combined with either ''common variable immunodeficiency'' or ''primary immunodeficiencies.'' Cases of AITP quoted in large series of patients with CVID were not included when clinical and laboratory data were not available.

The diagnosis of active autoimmune hemolytic anemia was defined as follows: a decrease of at least 2 g/dL in hemoglobin levels, with features of hemolysis (unconjugated hyperbilirubinemia and/or elevated lactate dehydrogenase and/or low serum haptoglobulin level) and a positive direct antiglobulin test and/or the presence of cold agglutinin in the serum and/or after the exclusion of other causes of acquired or hereditary hemolytic anemia. The diagnosis of autoimmune neutropenia required an absolute neutrophil count $<1000/mm^3$ on at least 2 separate occasions with normal bone marrow cytology and after the exclusion of drug-induced neutropenia.

RESULTS

Patient Characteristics (Table 1)

The data from 21 patients, 12 men and 9 women, who fulfilled the inclusion criteria were analyzed. Taking into account that 105 patients with CVID were followed in the participating centers at the time of analysis, the prevalence of AITP among patients with CVID was 20%. The median age at CVID diagnosis was 27 years (range, 10–74 yr) and the median age at AITP diagnosis was 23 years (range, 1 – 51 yr). The median duration of follow-up after AITP onset was 12 years (range, 1–31 yr) (Table 1). None of the patients was HIV- or hepatitis C (HCV)-positive. HCV RNA was detected by polymerase chain reaction (despite the absence of detectable antibodies against HCV) in only 1 of the 11 patients in whom this test was performed. In this patient, repeated liver biopsies showed no evidence of active chronic hepatitis, and the spleen was not enlarged.

Chronologic Relationship Between CVID and AITP (Table 1)

At time of AITP diagnosis, CVID had been diagnosed already in only 4 of the 21 patients (19%). When AITP occurred, 3 of these 4 patients were already being treated by intravenous immunoglobulin (IVIg) replacement therapy at

TABLE 1. Characteristics of 21 Patients with AITP and CVID (Present Series)

Patient/ Sex	Age at AITP/CVID Diagnosis (yr)	Follow-Up After AITP/CVID Diagnosis (yr)	Platelet Count at Diagnosis (x 10^9/L)	Lowest Platelet Count (x 10^9/L)	IgG Level (g/L)*	IgM Level (g/L)*	IgA Level (g/L)*	Anti-Platelet Antibodies	Direct Antiglobulin Test (specificity)	ANA/ aCl	Other Autoimmune Disorder
1/M	24/26.5	2.5/0.5	32	5	0.9	0.08	0.11	ND	+ (IgG)	–/–	None
2/M	31/28	1/4	10	10	4.0	0.4	0.70	ND	–	–/–	None
3/F	33/31	2/4	30	8	1.4	0.06	0.90	–	–	–/–	AIN, Thyroiditis
4/F	42/42	20/20	40	35	3.0	0.11	0.27	+	+ (IgG + Ct)	–/–	AIHA
5/M	20/21	6/5	36	36	5.0	0.73	0.03	–	–	–/–	None
6/F	41/41.5	4/3.5	50	50	3.0	0.06	0.05	+	+ (IgG)	–/–	None
7/M	21/23	18/16	20	5	2.6	0.12	0.04	+	+ (IgG + Ct)	–/ND	AIHA, AIN, celiac disease
8/M	7/17	12/2	14	14	5.0	0.26	0.6	+	+ (IgG)	–/–	AIHA
9/F	45/46	3/2	2	2	4.4	0.28	0.56	ND	ND	ND/ND	None
10/F	10/10	12/12	11	11	3.5	0.08	2.0	+	+ (IgG)	–/ND	None
11/M	15/14	9/10	11	11	4.5	3.4	0.06	+	+ (IgG)	–/ND	AIHA, AIN, Uveitis
12/F	22/35	28/15	20	20	4.4	0.50	0.1	ND	–	–/ND	None
13/M	1/19	23/5	50	50	4.7	0.40	0.5	–	–	–/ND	None
14/M	51/59	27/5	5	5	4.0	0.10	2.8	–	+ (IgG)	–/ND	AIHA
15/F	50/74	29/5	15	15	4.7	0.96	0.30	+	–	–/ND	AIN, vitiligo
16/M	18/18	9/9	26	19	1.0	0.13	0.01	–	–	–/–	None
17/M	49/33	1/7	45	45	3.7	0.40	1.1	ND	–	–/ND	None
18/M	50/63	14/1	37	37	4.6	0.89	0.55	–	–	–/–	IDDM, vitiligo
19/F	5/15	18/8	15	15	0.5	0.09	0.07	–	+ (IgG + Ct)	–/–	AIHA
20/M	14/14	31/31	18	18	2.5	4.0	0.3	ND	+ (IgG)	–/–	AIHA, celiac disease
21/M	9/16	9/1	9	9	2.1	0.24	0.13	ND	ND	–/–	AIN

Abbreviations: ND = not determined; ANA = antinuclear antibodies; aCl = anticardiolipin antibodies; AIHA = autoimmune hemolytic anemia; AIN = autoimmune neutropenia; IDDM = insulin–dependent diabetes mellitus; Ct = complement; + = positive; – = negative.

*Normal values for Ig levels: IgG, 6–12 g/L; IgM, 0.5–2.4 g/L; IgA, 0.7–4.1 g/L.

a mean dose of 0.4 g/kg body weight every 3 weeks. AITP preceded the diagnosis of CVID in 13 other cases (62%); the median delay between the diagnoses was 9 years (range, 0.5–18 yr). Among these 13 patients, serum protein electrophoresis was performed at AITP diagnosis in a single patient and showed no abnormalities. Lastly, CVID and AITP were diagnosed concomitantly in 4 patients (19%). The diagnosis of CVID was made ''fortuitously'' on serum protein electrophoresis in 3 patients, whereas CVID was highly suspected by a previous history of recurrent upper respiratory tract infections in the fourth.

Characteristics of AITP at Onset (Table 1)

The median platelet count at AITP diagnosis was 20×10^9/L (range, $2–50 \times 10^9$/L). AITP was diagnosed during or a few days after an infection in 3 cases (rubella = 1, tonsillitis = 1, intestinal infection due to *Salmonella typhi murium* = 1). Four of the 11 patients with a platelet count $\leq 20 \times 10^9$/L at onset had both cutaneous and mucosal bleeding symptoms (that is, gum and/or nose bleeding and/or menorrhagia); a life-threatening hemorrhagic syndrome with a decrease in hemoglobin level >2 g/dL was observed in a single case (Patient 3). During follow-up, a nonfatal intracranial hemorrhage occurred after head trauma (platelet count $<30 \times 10^9$/L) in another patient.

Fourteen of the 21 patients were tested for the presence of circulating antiplatelet antibodies by a standard indirect immunofluorescence method, and a positive result was found in 7 (50%) (see Table 1). Antibodies directed toward the platelet glycoprotein IIb/IIIa complex were detected in 2 of the 3 patients tested by means of monoclonal antibodies immobilization platelet assay (MAIPA).

Characteristics of CVID and Associated Conditions (Tables 1 and 2)

The mean immunoglobulin level at time of CVID diagnosis was 360 mg/dL (±180); the mean lymphocyte count was 1250 (±1408). The levels of IgG, IgA, and IgM at time of CVID diagnosis are shown in Table 1. The prevalence of associated conditions in this series and in the largest series of patients with CVID reported in the literature[4] are summarized in Table 2.

Associated Autoimmune Diseases

Besides AITP, 11 patients (52%) had at least 1 other autoimmune manifestation, including autoimmune hemolytic anemia (n = 7), autoimmune neutropenia (n = 5), celiac disease (n = 2), vitiligo (n = 2), unclassified chronic polyarthritis (n = 1), autoimmune thyroiditis (n = 1), type I diabetes (n = 1), and relapsing anterior uveitis (n = 1) (see Table 1). Autoimmune hemolytic anemia was the most frequently associated autoimmune disorder, occurring in 33% of the patients. Moreover, 2 other patients (Patients 6 and 10) had a positive direct antiglobulin test without hemolysis. Autoimmune hemolytic anemia occurred 2–12 years after AITP in 5 cases and preceded the diagnosis of AITP in the 2 remaining cases (by 2 and 14 years, respectively). In 2 of these patients, the hemoglobin level fell below 5 g/dL at the onset of autoimmune hemolytic anemia. Neither antinuclear nor anticardiolipin antibodies were detected in the patients who were tested (see Table 1).

Management and Outcome of AITP (Table 3)

AITP did not require any specific therapy in 4 patients (Patients 5, 6, 13, 17): the platelet count rose spontaneously above 50×10^9/L in 2 of them, and 2 patients with a platelet count $<50 \times 10^9$/L never had any bleeding symptoms (Patients 5 and 17, Tables 1 and 3). During follow-up, the platelet count remained $<100 \times 10^9$/L in 3 of these 4 patients, whereas a complete remission occurred in the fourth (Patient 17) after the initiation of IVIg replacement therapy.

Seventeen patients (81%) received at least 1 treatment for AITP (see Table 3). As first-line or second-line therapy,

TABLE 2. Prevalence of Associated Conditions (Other Than AITP) Associated with CVID

Associated Condition	No. of Patients (%) (Present Series)	No. of Patients (%) From the Largest Series in Literature*
Recurrent bacterial infections of the respiratory tract	20/21 (95%)	242/248 (97%)
Chronic lung disease	3/21 (14%)	68/248 (27%)
Benign lymphoproliferative disease (lymphadenopathy ± splenomegaly)†	16/21 (76%)	NA
Non-Hodgkin lymphoma	2/21 (9%)	19/248 (7.5%)
Autoimmune diseases (other than AITP)	11/21 (52%)	55/248 (23%)
Intestinal manifestations (chronic diarrhea, malabsorption)‡	10/21 (47%)	NA
''Sarcoid-like'' granulomatous disease§	6/21 (28%)	21/248 (8%)

*Reference 4.
†Including isolated or diffuse lymphadenopathy, splenomegaly, or both, without histologic features of malignancy.
‡Including chronic diarrhea, infectious diarrhea due to *Giardia lamblia*, malabsorption, or protein-losing enteropathy.
§Histologically proven ''sarcoid-like'' granulomatous disease without evidence of mycobacterial infection.

13 patients received corticosteroids alone, 4 were given IVIg alone at a dose $\geq$1 g/kg, and 4 patients received both treatments in combination (see Table 3). The treatment of AITP, response to therapy, and outcome are summarized in Table 3; the global management of the 17 patients who required treatment is shown in Figure 1.

Corticosteroids Alone (n = 13)

Eleven patients were treated with prednisone at a mean daily dose of 1 mg/kg for at least 3 consecutive weeks as a first or second-line of therapy. Two patients first received methylprednisolone intravenously (Patients 1 and 2) at 500 mg per day for 3 consecutive days before oral prednisone. Prednisone was given for fewer than 8 weeks in 4 patients (Patients 1, 2, 7, 19), 3 patients (Patients 3, 10, 19) were treated with prednisone for more than 6 months for either systemic granulomatosis or associated autoimmune hemolytic anemia, and the duration of prednisone could not be assessed retrospectively in 6 cases. After a mean follow-up of 139 months (±141 SD), 6 of the 13 patients (46%; Patients 1, 2, 9, 10, 18, 20) achieved a durable partial response or complete response while requiring no additional treatment other than Patient 1, who was retreated with steroids for a short time in the case of transient relapse and Patient 10, who was still being treated for an associated hepatic granulomatous disease (see Table 3).

Eleven of the 13 patients (84%) were receiving IVIg substitutive therapy while on prednisone.

Intravenous Immunoglobulins (n = 8)

To treat AITP, 8 patients received IVIg at doses of 1–2 g/kg either alone (Patients 9, 15, 16, 21) or in combination with steroids (Patients 2, 3, 8, 11). IVIg given alone led to 1 complete response (Patient 21), 1 transient partial response (Patient 16), and 1 failure (Patient 15). Infusion had to be stopped promptly in Patient 9 since she complained of headache, feeling flush, and fever. Given in combination with steroids, IVIg led to 1 complete response (Patient 11), 1 transient partial response (Patient 8) and 2 failures (Patients 2, 3). Patient 2 was diagnosed with aseptic lymphocytic meningitis within 7 days after IVIg. In total, a short-term response (partial response or complete response) was obtained after IVIg in 4/8 cases (50%); Patient 21 was the only patient with a lasting response (see Table 3).

Splenectomy

Four patients underwent splenectomy for AITP a median of 2 years (2 mo to 13 yr) after AITP onset; 2 achieved a complete response and 2 failed to respond. Two additional patients (Patients 4, 11) underwent splenectomy for associated refractory autoimmune hemolytic anemia (Evans syndrome); before the procedure the platelet count was 61 $\times$ 10^9/L in Patient 4 (complete response after splenectomy) and normal in Patient 11 (see Table 3). With a mean follow-up of 5.6 years after the surgical procedure, none of the 6 patients who underwent splenectomy had a life-threatening bacterial infection due to *Streptococcus pneumoniae* or any other encapsulated bacteria. Two of the 6 patients had long-term prophylaxis with oracillin.

Other Treatments

Three of the 17 patients treated (17%) needed additional therapies for AITP to achieve at least a partial response (Patients 3, 15, 16), and 4 patients needed additional treatments (including danazol and/or azathioprine and/or cyclophosphamide) for associated autoimmune hemolytic anemia (Patients 4, 7, 11, 19) (see Table 3).

The alternative treatments patients received for AITP and the responses are shown in Table 3. Liver toxicity (increase in transaminases level) leading to the interruption of treatment was observed in 2 patients treated with danazol (Patients 3, 4), and hemolytic anemia (hemoglobin level <8.5 g/dL) was observed after dapsone (Patient 16). Lastly, Patient 3, who had life-threatening AITP and an underlying chronic renal insufficiency, complained of a chronic painful peripheral neuropathy after receiving 3 courses of vincristine at 1.5 mg each. She did not respond to splenectomy but then achieved a partial response after 5 courses of intravenous pulses of cyclophosphamide.

Infectious Complications

During follow-up, 9 episodes of severe infections (requiring hospitalization and intravenous treatment) occurred in 6 of the 17 patients (35%) treated for AITP, 3 of which were fatal. These infectious complications occurred a mean of 17 years after AITP diagnosis. Their characteristics are summarized in Table 4.

AITP Global Outcome and Mortality

The course of AITP was chronic (duration >6 mo) in all but 2 patients (90%). Patient 17 achieved a lasting complete response after the initiation of IVIg replacement therapy alone, and Patient 21 had a lasting complete response after a single course of IVIg given at a dose of 1.2 g/kg. On the other hand, AITP was particularly severe and ''refractory'' in 2 patients (Patients 3, 15). However, at the last evaluation, after a median follow-up of 12 years, 20/21 patients (95%) were in partial or complete remission: 14 patients (66%) were in treatment-free complete or partial remission, and 6 patients (28%) were in remission while on prednisone ($\leq$20 mg/d) and/or azathioprine for chronic AITP (n = 4), autoimmune hemolytic anemia (n = 1), or granulomatous disease (n = 1). The final patient (Patient 14) was not in remission but was left without treatment since his platelet count was >30 $\times$ 10^9/L without any bleeding manifestations (see Table 3).

Five patients (24%) had died at the time of analysis. AITP was in remission at the time of death in all patients.

TABLE 3. Management and Outcome of AITP (Present Series)

Patient	First-Line Therapy: Short-Term Response	Second-Line Therapy: Response	Third-Line Therapy: Response	Other Therapy	Follow-Up After AITP Onset/Platelet Count and Treatment at Last Evaluation
1	HDMP + PRDN: CR	3 Relapses retreated with PRDN			2.5 yr/300 × 10^9/L with PRDN at 20 mg/d
2	IVIg + PRDN: failure	HDMP + PRDN: short-term CR and long-term PR			1 yr/70 × 10^9/L, no treatment (deceased)
3	IVIg + PRDN: failure	Splenectomy: failure	VCR: failure and peripheral neuropathy	Danazol: toxic hepatitis IV cycloph. (5 courses): PR then replaced by Azath.: sustained PR	2 yr/75 × 10^9/L, PR with Azath. + PRDN 5 mg/d
4	PRDN: not evaluable (lost to follow-up)	Danazol + PRDN for AIHA (hepatitis after danazol)	Splenectomy for relapsing corticodependant AIHA (platelet count = 61 × 10^9/L prior to splenectomy)		19 yr/404 × 10^9/L yr after splenectomy without treatment
5	None				16 yr/50–100 × 10^9/L, no treatment
6	None				6 mo/100 × 10^9/L, no treament (deceased)
7	PRDN: PR	Danazol + PRDN for AIHA	Azath. for relapsing AIHA		18 yr/60–100 × 10^9/L with PRDN at 10 mg/d and Azath. 100 mg/d
8	PRDN + IVIg: PR	Splenectomy: CR			12 yr/>150 × 10^9/L, no treatment
9	IVIg: intolerance	PRDN: CR			3 yr/193 × 10^9/L, no treatment
10	PRDN: transient PR	1 Relapse retreated with PRDN (PR)			12 yr/50–100 × 10^9/L with PRDN at 20 mg/d (hepatic granulomatosis)
11	PRDN + IVIg: CR	PRDN for AIHA	Splenectomy for AIHA	Azath. for relapsing AIHA	9 yr/>150 × 10^9/L, no treatment
12	PRDN: PR	Azath. + PRDN: PR	IVIg + PRDN: CR		28 yr/150 × 10^9/L with PRDN at 5 mg/d (deceased)
13	None				23 yr/>50 × 10^9/L, no treatment
14	PRDN: PR	2 Relapses retreated with PRDN: PR			27 yr/33 × 10^9/L, relapse without treatment
15	PRDN: failure	IVIg: failure	Azath. + PRDN: failure	Splenectomy: failure IFNγ + plasmapheresis: CR	29 yr/>150 × 10^9/L, no treatment
16	PRDN: PR	IVIg: PR	Danazol: PR	Dapsone: PR and stopped (hemolysis) VCR: PR Splenectomy: CR	9 yr/>150 × 10^9/L, no treatment
17	None				1 yr/>150 × 10^9/L after initiation of IVIG supportive therapy alone
18	PRDN: PR				14 yr/>75 × 10^9/L, no treatment
19	PRDN: PR	PRDN for AIHA	Cycloph. for relapsing AIHA	Azath. for relapsing AIHA	18 yr/294 × 10^9/L with Azath. for AIHA (deceased)
20	PRDN: PR				31 yr/80 × 10^9/L, no treatment (deceased)
21	IVIg: CR				9 yr/50–160 × 10^9/L, no treatment

Abbreviations: IVIg = intravenous immunoglobulins; PR = partial response; CR = complete response; cycloph. = cyclophosphamide; PRDN = oral prednisone; HDMP = high doses of intravenous methylprednisolone; VCR = vincristine; IFNγ = gamma interferon; Azath. = azathioprine.

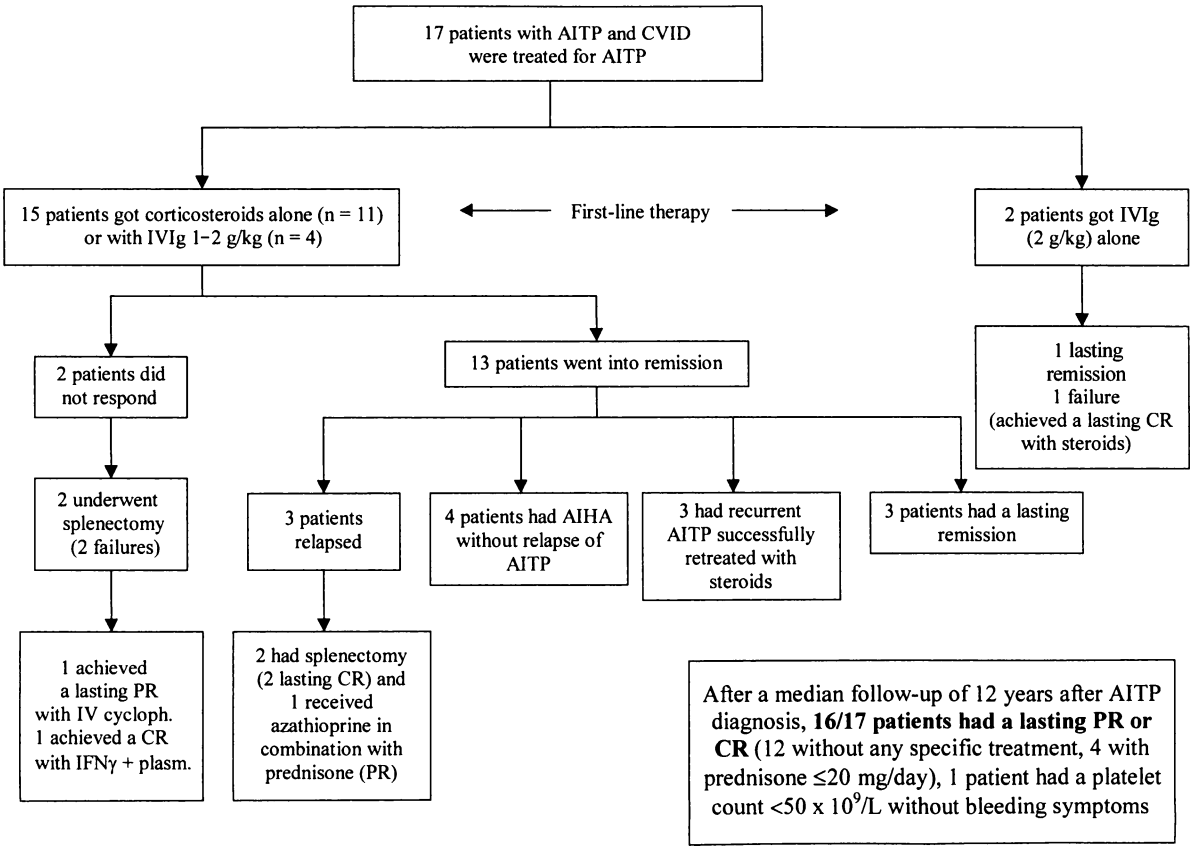

FIGURE 1. Global management of autoimmune thrombocytopenic purpura and response in the 17 patients treated. Abbreviations: AIHA = autoimmune hemolytic anemia; CR = complete response; PR = partial response.

The causes of death were severe infections in 3 cases (Patients 12, 19, 20; see Table 4); relapsing cerebral venous thrombosis in 1 case (Patient 2); and fulminant hepatitis of unknown origin in the last case (Patient 6).

DISCUSSION

According to the reports in the literature with a large number of patients, AITP occurs in 0 to 25% of the patients with CVID and represents up to 50% of the associated cases of autoimmune disease[4,5,12,13,14,19]. However, the characteristics of AITP in this setting are not well known. By reviewing the literature we were able to find only 14 distinguished cases of AITP in patients with CVID for whom at least some clinical and laboratory data were available[1,2,6,16,17,18,20,21,25]. Additional data from 18 patients followed at a single institution have also been partially reported in a 2002 review focusing on hematologic complications in primary immune deficiencies[3].

To determine better the features and outcome of AITP in patients with CVID, we analyzed the data of 21 patients in the current series. To avoid other causes of thrombocytopenia, only patients with a platelet count $<50 \times 10^9$/L on at least 2 separate occasions and a normal bone marrow were included in our series. Furthermore, none of the patients had chronic active hepatitis C or features of portal hypertension and/or hypersplenism at the time of AITP diagnosis. Unlike what is usually observed in ''idiopathic'' or primary AITP in which women are preferentially affected (female:male ratio, 1.7 to 2.0:1)[7,8], when patients from our series and from the literature were considered, 60% of the patients with CVID and AITP were male. This finding suggests that immunologic abnormalities found in CVID are the major single risk factor for developing AITP.

On the other hand, and unlike what was initially reported by Imbach et al[15], the initiation of IVIg supportive therapy (at 0.4–0.5 g/kg every 3 wk) did not prevent the occurrence or relapse of AITP in 3 patients from this series. In that, CVID-associated AITP looks like primary AITP, for which IVIg is notoriously ineffective in adults when given at only 0.5 g/kg and does not influence the natural history of the disease when administered repeatedly, even at higher doses (that is, 1–2 g/kg every 3 wk)[10].

It is noteworthy that in most of the cases from this series, regardless the age of the patients, the diagnosis of AITP revealed or preceded the diagnosis of CVID. Among the 32 patients previously reported in the literature, AITP

TABLE 4. Severe Infections During or After Treatment for AITP

Patient, Sex/Age at Time of Last Infection (yr)	Previous Treatment for AITP	Associated Condition	Ongoing Treatment for AITP at Time of Infection and Dose	IVIg Substitutive Therapy at Time of Infection	Type of Infection (Time After AITP Onset)	Outcome
3) F/33	Prednisone, IVIg	Chronic renal insufficiency (granulomatosis)	Prednisone 1 mg/kg per day	Yes	Septicemia due to MRSA (1 mo)	Recovery
12) F/35	Prednisone, azathioprine	Hepatic granulomatous disease, lymphoid hyperplasia, chronic respiratory disease	Prednisone 20 mg/d + azathioprine 150 mg/d	No	1. Septicemia due to *Enterobacter sp*. (5 yr)	Recovery
			Prednisone 7 mg/d	Yes	2. Pulmonary aspergillosis (24 yr)	Recovery with IV fungizone then itraconazole
			Prednisone 5 mg/d	Yes	3. Pneumonia due to *Pseudomonas aeruginosa* (27 yr)	Died from respiratory failure
14) M/53	Prednisone	AIHA	None	No	1. Pneumonia due to *Streptococcus pneumoniae* (8 yr) revealing the CVID	Recovery
			Prednisone 10–40 mg/d for relapsing ITP/AIHA	Yes	2. Septicemia and arthritis due to *Salmonella sp*. (11 yr)	Recovery
15) F/77	IVIg, prednisone, azathioprine splenectomy, IFNγ + plasmapheresis	Autoimmune neutropenia, lymphoid hyperplasia	None	Yes	*Toxoplasma gondii*-related uveitis (25 yr)	Recovery
19) F/23	Prednisone	AIHA, celiac disease, lymphoid hyperplasia	Azathioprine	Yes	Septic shock due to *Haemophilus influenzae* and *Strep. pneumoniae* septicemia (18 yr)	Died from sepsis
20) M/45	Prednisone, oral cycloph. and azathioprine for AIHA	AIHA, hepatic granulomatous disease, celiac disease	None	Yes	Septic shock due to *Citrobacter freundii* septicemia (35 yr)	Died from intracerebral hemorrhage complicating sepsis and disseminated intravascular coagulation

Abbreviations: See previous tables. MRSA = methicillin-resistant *Staphylococcus aureus*.

was diagnosed before CVID in 26 of the 32 cases (81%); both diseases were diagnosed simultaneously in 4 cases (12.5%); and CVID preceded the onset of AITP in only 2 cases. This observation should encourage clinicians to measure serum immunoglobulins at AITP diagnosis, even in the absence of previous infectious manifestations suggesting a primary immunodeficiency. An early diagnosis of CVID may indeed influence the outcome of the disease by preventing the occurrence of recurrent infections and long-term pulmonary complications[27]. In addition, testing for IgA levels is strongly recommended in AITP since patients with IgA deficiency, and therefore with CVID, might develop anti-IgA antibodies and experience severe reactions to blood products including IVIg[11]. AITP lasted more than 6 months in all cases, but 2 in this series and 17 of the 21 patients required a specific treatment to increase the platelet count. However, none of the patients had truly chronic refractory AITP, since at the end of follow-up, 20 of them (95%) were in remission (platelet count $>50 \times 10^9$/L) and the final patient, whose platelet count was 33×10^9/L, was left without treatment in the absence of any bleeding symptoms (see Table 3). Although the number of patients was too small to draw final conclusions, the response rate to IVIg given alone at 1–2 g/kg or in combination with corticosteroids was disappointing compared to that usually observed in primary AITP[7]. In contrast, corticosteroids alone seem to be an effective treatment, since, based on our experience, they lead to a lasting response in approximately half the patients.

Regarding the management of AITP in patients with CVID in the literature, partial data were available in the 18 patients from the series of Cunningham-Rundles[3] and in 9 of the 14 single case reports. Overall, as a first-line therapy, 22 of these 27 patients (81%) received corticosteroids with or without IVIg at 2 g/kg, 14 of whom (63%) achieved a lasting response. Four patients received IVIg alone at 2 g/kg, and only 1 (25%) achieved a transient response. Based on our experience and that in the literature, we believe a short course of corticosteroids is worth trying as a first-line therapy in patients with CVID who have severe thrombocytopenia ($<30 \times 10^9$/L) and bleeding manifestations. Four patients from the current series and 8 from the literature underwent a splenectomy for AITP, while 2 additional patients underwent splenectomy for associated autoimmune hemolytic anemia. After splenectomy, a lasting response was obtained in 8 of the 12 patients with AITP (66%). Only 1 of the 14 splenectomized patients had a life-threatening infection after splenectomy, and all of them were alive at the time of analysis. In the 2 largest series in the literature[4,13] including a total of 498 patients with CVID, 30 patients underwent splenectomy for various reasons (including autoimmune hemolytic anemia in 9 cases and AITP in 6). Although the autoimmune disease resolved after the procedure in most of the cases[4], 3 of these patients (10%) died from pneumococcemia soon after splenectomy, and 5 patients (16%) had at least 1 postoperative severe infection, including pneumococcal sepsis in 2 cases (1 and 2 years after the procedure, respectively). Therefore, although splenectomy was safe in our experience, the underlying immunodeficiency cannot be underestimated, and this procedure should be considered only for those rare patients with chronic AITP who have a platelet count $<20–30 \times 10^9$/L and bleeding symptoms.

Both the prevalence and the kinds of associated autoimmune conditions seen in patients with CVID and AITP were remarkable. The frequency of autoimmune diseases was increased at least twofold compared with the usual rates observed in the large series of patients with CVID[4] (see Table 2). In addition, autoimmune hemolytic anemia (Evans syndrome) and autoimmune neutropenia were particularly frequent in the subgroup of patients with AITP (39% in the current series, and as many as 63% of the cases reported in literature). We note that, as previously reported[3], while patients with CVID are unable to produce specific antibodies in response to infecting microorganisms, they paradoxically retain the ability to produce autoantibodies, directed against platelet, erythrocyte, and/or neutrophil membrane antigens rather than nuclear or tissue antigens. Although a hypothesis has been suggested[3], the relationship between immunodeficiency and autoimmunity is far from being understood.

Besides recurrent infections of the upper respiratory tract, which occurred in 95% of the patients in the current series, the frequency of other manifestations, such as non-malignant lymphoproliferative disorder (76%) and ''sarcoid-like'' granulomatous disease (28%), was also unexpectedly high when compared with the largest series reported in literature (20% and 8%–10%, respectively)[4,12,13,14,20]. This finding suggests that among patients with CVID, a notoriously heteregeneous syndrome, a subgroup of patients could share a particular ''phenotype'' with a higher susceptibility towards lymphoproliferation and autoimmune manifestations. Whether these manifestations could be triggered by a common environmental antigen remains to be determined.

In conclusion, since AITP frequently reveals or precedes the diagnosis of CVID, patients diagnosed with AITP should be tested for immunoglobulin subtype levels regardless their age. Performing a direct antiglobulin test and looking for hemolysis and neutropenia is also important since autoimmune hemolytic anemia (Evans syndrome) and autoimmune neutropenia are frequent in this subgroup of patients and might worsen the prognosis. In patients with CVID, the course and outcome of AITP do not seem to be influenced by IVIg supportive therapy, and management of AITP specifically is often required. The treatment of AITP

must take into consideration the increased risk of infections in patients with CVID, and as recommended in idiopathic AITP, only patients with a platelet count $<30 \times 10^9$/L and with bleeding symptoms must be treated. In our experience, splenectomy was safe but should be performed only as a last resort. Future advances in basic research could help us understand how defects in immunoglobulin production give rise to antibody-mediated autoimmune diseases.

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