CASE REPORT

Successful Use of Rituximab in Refractory Idiopathic Thrombocytopenic Purpura in a Patient With Common Variable Immunodeficiency

M Al-Ahmad,[1] M Al-Rasheed,[2] A Al-Muhani[2]

[1]Department of Allergy, Al-Rashed Allergy center, Ministry of Health, Kuwait
[2]Department of Medicine, Mubarak Hospital, Ministry of Health, Kuwait

Abstract

Idiopathic thrombocytopenic purpura (ITP) is a common autoimmune disease in patients with common variable immunodeficiency (CVID). We describe a 36-year-old woman with CVID. The clinical course of her disease was complicated by bronchiectasis, antiphospholipid antibody syndrome, and portal vein thrombosis. She developed recurrent attacks of ITP refractory to high doses of corticosteroid, intravenous immunoglobulin (IVIG), and splenectomy. She received a total of 5 doses of rituximab (375 mg/m^2) and achieved an immediate and persistent response. Therapy was well tolerated. Her platelet count remained above 370 000/µL for 8 months of follow-up, despite repeated infections. During this period the patient remained off corticosteroids and on continuous IVIG replacement therapy.

Key words: Rituximab. Idiopathic thrombocytopenic purura. Common variable immunodeficiency.

Resumen

La púrpura trombocitopénica idiopática (PTI) es una enfermedad autoinmunitaria frecuente en pacientes con inmunodeficiencia común variable (IDCV). En el presente estudio se describe el caso de una mujer de 36 años de edad con IDCV. La evolución clínica de la enfermedad presentaba complicaciones por bronquiectasia, síndrome antifosfolipídico y trombosis de la vena porta. La paciente sufrió ataques recurrentes de PTI resistentes al tratamiento con dosis elevadas de corticoesteroides, inmunoglobulina intravenosa (IGIV) y esplenectomía. Tras la administración de 5 dosis de rituximab (375 mg/m^2), la paciente registró una respuesta inmediata y persistente. El tratamiento fue bien tolerado. El recuento de plaquetas se mantuvo por encima de 370.000/µl durante 8 meses de seguimiento, a pesar de producirse repetidas infecciones. Durante este período, la paciente no recibió corticoesteroides y se sometió a terapia sustitutiva continua con IGIV.

Palabras clave: Rituximab. Púrpura trombocitopénica idiopática. Inmunodeficiencia común variable.

Introduction

Common variable immunodeficiency (CVID) is the most common symptomatic primary antibody deficiency in adulthood, and approximately 23% of patients with CVID develop autoimmune disease [1]. Autoimmune cytopenia, particularly idiopathic thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) are the most frequently diagnosed autoimmune diseases in CVID [2-4]. The much lower prevalence of ITP and AIHA in the general population (1.0-12.5 cases/100 000 people/y [5] and 1-3 cases/100 000 people/y [6]) than in patients with CVID indicates an exceptionally high susceptibility to autoimmunity in patients with CVID. Those who develop ITP generally respond well to standard treatment regimens, including corticosteroids and IVIG [2]. However, not infrequently, ITP is refractory to treatment. The underlying etiology of autoimmune disease in CVID is unknown.

Case Description

A 36-year-old woman presented with multiple sinopulmonary infections and lung abscesses that partially responded to antibiotics. A computed tomography scan of her chest and abdomen showed evidence of multiple lymph node enlargement, bronchiectatic changes in the right middle and lower lobes, and splenomegaly. Lymph node biopsy showed reactive changes only. She had an immunoglobulin (Ig) G level of 0.5 g/L (reference range, 6.0-16.0 g/L), an IgA level of 0.35 g/L (reference range, 0.89-4.46 g/L), and an IgM level of 0.2 g/L (reference range, 0.5-1.9 g/L). Accordingly, she was diagnosed with CVID and kept on regular IVIG at a dose of 600 mg/kg every 3 weeks. The course of her disease was complicated by antiphospholipid antibody syndrome, which was diagnosed after determination of positive titers for anticardiolipin antibody, ß$_2$-glycoprotein antibody, and antiphospholipid antibody.

She had an episode of portal vein thrombosis and was therefore on lifelong anticoagulation therapy. After screening for viral infection, she was found to have persistent viremia caused by Epstein-Barr virus (EBV) and cytomegalovirus (CMV), although serology results for HIV-1 and HIV-2, hepatitis B surface antigen, and anti–hepatitis C virus (HCV) antibody were negative, and the VDRL test was nonreactive. The results of screening for other autoimmune markers including antinuclear antibodies (ANA), anti-dsDNA antibodies, antineutrophil cytoplasmic antibody (ANCA-C), protoplasmic-staining antineutrophil cytoplasmic antibody (ANCA-P), smooth muscle antibody, and antimitochondrial antibody were negative.

Two years after diagnosis of CVID, her platelet count dropped to 9000/µL. However, the peripheral blood smear showed a high platelet count with no evidence of abnormal cells, thus supporting the diagnosis of ITP. She was treated with repeated courses of high-dose IVIG and corticosteroids, with no response. She achieved complete remission (CR) after splenectomy.

Six months later, she experienced a relapse of her ITP after infection with varicella-zoster virus. She was admitted to hospital and treated with intravenous acyclovir, high-dose IVIG, and methylprednisolone pulse therapy. Her platelet count remained in the range of 10 000/µL to 15 000/µL after discharge and she was prescribed prednisolone maintenance treatment (1 mg/kg).

Other treatment options for refractory ITP were proposed, including immunosuppressive agents, danazol, and vincristine, but the patient refused because of the safety profile of these drugs. She finally agreed to be treated with rituximab, at a dose of 375 mg/m^2, once weekly for 4 weeks. There was no response to treatment 1 month after the fourth dose of rituximab. A fifth dose was administered and the patient achieved an immediate and persistent response. Therapy was well tolerated and B lymphocytes were depleted from peripheral blood (<0.01% B lymphocytes by flow cytometry). Her platelet count remained above 370 000/µL for 8 months of follow-up, despite repeated viral and bacterial infections. During this period, the patient remained off corticosteroids and on continuous replacement therapy with IVIG.

Discussion

ITP is one of the most common causes of thrombocytopenia in adults and children [4]. Although the etiology of ITP remains unclear, genetic and acquired factors are believed to play a significant role in the acquisition of this disease [5]. ITP can be primary (idiopathic) or secondary to other diseases, such as lymphoproliferative disorders, viral infections, connective tissue disorders, and immunodeficiency. The pathogenesis of ITP is thought to be mediated by abnormalities in B lymphocytes and T lymphocytes [6].

Standard treatment of ITP in adults includes corticosteroids, splenectomy, gammaglobulin, immunosuppressive agents, and danazol [7]. In a substantial number of patients, the disease is refractory to first-line therapy with corticosteroids. Second-line therapy with splenectomy has been shown to induce complete remission in two-thirds of patients and partial remission in 15% [4]. Third-line therapy with immunosuppressive agents has achieved an overall survival rate of 20% to 50% [8,9]. Fourth-line therapy with danazol, vitamin C, colchicine, and plasmapheresis is largely unsuccessful.

Rituximab is a chimeric murine/human monoclonal antibody against the CD20 antigen expressed on pre-B lymphocytes and mature B lymphocytes. It was initially created to treat CD20$^+$ B-cell lymphoma.

There is a growing body of research (mainly case reports and case series) suggesting that rituximab can be used to treat refractory ITP, AIHA, and other autoimmune diseases with varying degrees of success [10-13].

We describe a 36-year-old woman with refractory ITP secondary to CVID.

Rituximab at 375 mg/m^2 /wk for a total of 4 weeks failed to improve her platelet count, and she did not achieve complete remission until the fifth dose of rituximab. She sustained a platelet count above 370 000/µL, and B lymphocytes <0.2% during the follow-up period.

Only 3 case reports examine the use of rituximab in the treatment of ITP secondary to CVID. In 2 cases, rituximab was administered at 375 mg/m^2/wk for a total of 4 consecutive weeks and the patient achieved complete response with normalization of the platelet count [14,15]. In the third case, the same dose was used on a weekly basis for a total of 5 weeks, and the patient achieved a partial response [16]. Our findings are consistent with those of other studies [14], which demonstrated that treatment with rituximab can induce prolonged B-cell depletion.

We observed concomitant resolution of persistent EBV and CMV viremia and complete normalization of autoimmune antibody titers including antiphospholipid antibody, anticardiolipin antibody, and anti–ß$_2$-glycoprotein (Table). We attribute these results to a possible improvement in T-cell function, a process that has been emphasized recently in the mechanism of action of rituximab [17].

A number of clinical trials have shown that rituximab, when used in the treatment of ITP, works through regulation of B-cell and T-cell function. Stasi et al [17] have shown that T-cell abnormalities, including elevated T_H1/T_H2 cytokine ratios, elevated CD4-positive T cell–associated Bcl-2/Baxm RNA levels, and oligoclonal T-cell expansion were completely

Table. Effect of Rituximab on Different Laboratory Parameters

Laboratory Parameter	Pretreatment With Rituximab	Posttreatment With 5 Doses of Rituximab
Antiphospholipid syndrome	Positive	Negative
Anticardiolipin antibody: IgM	17 MPL U/mL (reference value, <11)	5 MPL U/mL
Anticardiolipin antibody: IgG	5 GPL U/mL (reference value, <23)	5 GPL U/mL
ß$_2$-glycoprotein antibody: IgG, IgM	23 IU (reference value, <8) 24 IU (reference value, <8)	4 IU 6 IU
C3, C4	Low, low	Normal, normal
CMV DNA by conventional PCR	Positive	Not detected
EBV DNA by conventional PCR	Positive	Not detected
Neutrophil count	0.25×10^9/L	3.48×10^9/L
Flow cytometry: B-cell counts	311 cells/µL (14.8%)	4 cells/µL (0.1%)
Anti-ANA antibody	Negative	Negative
Platelet count	4 × 103/µL	370 × 103/µL
Lymph node size on CT chest and abdomen	Enlarged	Regression

Abbreviations: ANA, antinuclear antibody; CMV, cytomegalovirus; CT computed tomography; EBV, Epstein-Barr virus; GPL, IgG phospholipid; Ig, immunoglobulin; MPL, IgM phospholipid; PCR, polymerase chain reaction

reversed after 3 months of therapy with rituximab. These effects on T-cell function may explain the normalization of antiphospholipid antibody titers (both anticardiolipin and ß$_2$-glycoprotein antibody), and a concomitant improvement in our patient's immune neutropenia. These effects may also explain the control of EBV and CMV viremia, since CD8$^+$ cytotoxic T cells are known to play a critical immunosurveillance role in the control of persistent EBV and CMV infection. For example, EBV-specific CD8$^+$ T cells can express interleukin (IL) 4, IL-10, and IL-13, which are involved in B-cell activation and proliferation [18].

Lymph node enlargement could be secondary to EBV infection and the return to normal size could be explained by reversal of EBV viremia. This explanation is further supported by the results of experiments in severe combined immunodeficiency mice engrafted with human peripheral blood lymphocytes, thus showing that the presence of T cells was required for the development of EBV-induced lymphoproliferative disease [19,20].

ITP is a common autoimmune disorder associated with CVID. Rituximab has proven to be an effective treatment for refractory cases of idiopathic ITP associated with CVID, and its role in improving T-cell and B-cell function should be further explored in order to fully understand the mechanism of rituximab in autoimmune disorders.

References

1. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol. 1999;92(1):34-48.
2. Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. Blood Rev. 2002;16(1):61-4.
3. Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH. Severe deficiency of switched memory B cells (CD27(+) IgM(−)IgD(−)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood. 2002;99:1544-51.
4. George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, Blanchette VS, Bussel JB, Cines DB, Kelton JG, Lichtin AE, McMillan R, Okerbloom JA, Regan DH, Warrier I. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996;88:3-40.
5. Gehrs BC, Friedberg RC. Autoimmune hemolytic anemia. Am J Hematol. 2002;69:258-71.
6. Coopamah MD, Garvey MB, Freedman J, Semple JW. Cellular immune mechanisms in autoimmune thrombocytopenic purpura: an update. Transfus Med Rev. 2003 Jan;17(1):69-80.
7. British Committee for Standards in Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children and in pregnancy. Br J Haematology. 2003;120:574-96.
8. Figueroa M, Gehlsen J, Hammond D, Ondreyco S, Piro L, Pomeroy T, Williams F, McMillan R. Combination chemotherapy in refractory immune thrombocytopenic purpura. Blood. 1991;81:3484-5.
9. Reiner A, Gernsheimer T, Slichter SJ. Pulse cyclophosphamide therapy for refractory autoimmune thrombocytopenic purpura. Blood. 1995;85:351-8.
10. Coiffer B, Lepage E, Briere J, Henbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, Reyes F, Lederlin P, Gisselbrecht C. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med. 2002;346:235-42.
11. Czuczman MS, Grillo-Lopez AJ, White CA, Saleh M, Gordon L, LoBuuglio AF, Jonas C, Klippenstein D, Dallaire B, Varns C. Treatment of patients with low grade B cell lymphoma with the combination of chimeric anti CD20 monoclonal antibody and CHOP chemotherapy. J Clin Oncol. 1999;17:268-76.
12. Stasi R, Stepa I, Forte V, Meo P, Amadori S. Variable patterns of response to rituximab treatment in adult with chronic idiopathic thrombocytopenic purpura. Blood. 2002;99:3872-3.
13. Zecca M, De Stefano P, Noobili B, Locatelli F. Anti CD 20 monoclonal antibody for the treatment of severe immune -mediated pure red cell aplasia and haemolytic anaemia. Blood. 2001;79:3995-7.
14. Wakim M, Shah A, Arndt PA, Garratty G, Weinberg K, Hofstra T, Church J. Successful anti-CD20 monoclonal antibody treatment

of severe autoimmune hemolytic anemia due to warm reactive IgM autoantibody in a child with common variable immunodeficiency. Am J Hematol. 2004;76(2):152-5.
15. El-Shanawany TM, Williams PE, Jolles S. Response of refractory immune thrombocytopenic purpura in a patient with common variable immunodeficiency to treatment with rituximab. J Clin Pathol. 2007;60:715-36.
16. Carbone J, Escudero A, Mayayo M, Ballesteros M, Perez-Corral A, Sanchez-Ramon S, Sarmiento E, Micheloud D, Fernandez-Cruz E. Partial response to anti-CD20 monoclonal antibody treatment of severe immune thrombocytopenic purpura in a patient with common variable immunodeficiency. Ann N Y Acad Sci. 2005;1051:666-71.
17. Stasi R, Del Poeta G, Stipa E, Evangelista ML, Trawinska MM, Cooper N, Amadori S. Response to B-cell–depleting therapy with rituximab reverts the abnormalities of T-cell subsets in patients with idiopathic thrombocytopenic purpura. Blood. 2007;110:2924-30.
18. Nazaruk RA, Rochford R, Hobbs MV, Cannon MJ. Functional diversity of the CD8 (+) T-cell response to Epstein-Barr virus (EBV): implications for the pathogenesis of EBV-associated lymphoproliferative disorders. Blood. 1998;91:3875-83.
19. Veronese ML, Veronesi A, D'Andrea E, Del Mistro A, Indraccolo S, Mazza MR, Mion M, Zamarchi R, Menin C, Panozzo M, Amadori A, Chieco-Bianchi L. Lymphoproliferative disease in human peripheral blood mononuclear cell-injected SCID mice. I. T lymphocyte requirement for B cell tumor generation. J Exp Med. 1992;176:1763.
20. Coles RE, Boyle TJ, DiMaio JM, Berend KR, Via DF, Lyerly HK. T cells or active Epstein-Barr virus infection in the development of lymphoproliferative disease in human B cell-injected severe combined immunodeficient mice. Ann Surg Oncol. 1994;1:405.

Manuscript received May 24, 2009; accepted for publication September 15, 2009.

Dr Mona Al-Ahmad

P.O. Box 72 Shamiya
Kuwait city, Kuwait
Zip code 71661
State of Kuwait
E-mail monaalahmad@yahoo.com

