American Journal of Internal Medicine
2015; 3(4): 156-159
Published online June 18, 2015 (http://www.sciencepublishinggroup.com/j/ajim)
doi: 10.11648/j.ajim.20150304.12
ISSN: 2330-4316 (Print); ISSN: 2330-4324 (Online)

Successful Rituximab Treatment of Autoimmune Hemolytic Anemia Caused by Both Warm Autoantibodies and Cold Agglutinin: A Case Report

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To cite this article:
Motoharu Shibusawa, Yoshirou Murai, Hisashi Tsutsumi. Successful Rituximab Treatment of Autoimmune Hemolytic Anemia Caused by Both Warm Autoantibodies and Cold Agglutinin: A Case Report. *American Journal of Internal Medicine.* Vol. 3, No. 4, 2015, pp. 156-159. doi: 10.11648/j.ajim.20150304.12

Abstract: This report describes a case which successfully treated with rituximab against autoimmune hemolytic anemia caused by both warm autoantibodies and cold agglutinin (mixed AIHA). A 52-year-old man with malaise was referred to our hospital in December 2002. A diagnosis of mixed AIHA was made. His clinical course showed that the hemolysis was mainly caused by cold agglutinin, with a possible contribution from the warm autoantibody. He was treated with prednisolone (PSL), Cyclosporine (CyA), and cyclophosphamide (CPA). The treatment with PSL, CyA, and CPA failed to stabilize the hemolysis caused by cold exposure in the winter season. In November 2013 (winter season), rituximab therapy (375 mg/m^2 weekly for four weeks) was started, and the hemolysis improved. The present case suggests that rituximab is useful against mixed AIHA. Further studies are warranted to establish the effectiveness of rituximab against mixed AIHA.

Keywords: Autoimmune Hemolytic Anemia, Rituximab, Mixed Autoimmune Hemolytic Anemia

1. Introduction

The effectiveness of rituximab against warm autoantibody positive autoimmune hemolytic anemia (warm-AIHA) and cold agglutinin positive AIHA (cold-AIHA) was reported previously. Hemolytic anemia positive for both warm autoantibody and cold agglutinin is called mixed AIHA. The effectiveness of rituximab against mixed AIHA is unclear. We report a case of mixed AIHA successfully treated with rituximab.

2. Case Presentation

A 52-year-old man with malaise was referred to our hospital in December 2002. He had a history of chronic renal dysfunction, diabetes mellitus, hypertension, and hyperuricemia. Laboratory data revealed normocytic anemia, high levels of reticulocytes (Reti), serum total bilirubin (Tbil), direct bilirubin (Dbil), lactate dehydrogenase (LDH), and Immunoglobulin G (IgG), low levels of haptoglobin. The results of a direct antiglobulin test were positive for complement components C3b and C3d. Cold agglutinins of the IgM type had a titer of 1:8192 (Table.1). A diagnosis of mixed AIHA was made based on the clinical course and laboratory data. His clinical course showed that the hemolysis was mainly caused by cold agglutinin, with a possible contribution from the warm autoantibody. On January 24, prednisolone (PSL) 60 mg/day for 12 days was initiated, and it subsequently followed a maintenance dose of 20–30 mg/day. His Hb level gradually increased and rose to 10.6 g/dL on March 6, and PSL was gradually decreased and discontinued because of improvement in anemia (Hb 14.9 g/dL) on August 20. On 23 January 2004, this anemia worsened: his Hb level dropped to 11.3 g/dL and Reti level rose to 3.15 %. He was hospitalized and treated with steroid pulse therapy (methylprednisolone 1000 mg/day) from 25 to 27 February 2004. Cyclosporine (CyA) 200 mg/day was started. CyA was discontinued in May 2005. He quit visiting our hospital in September 2009. In January 2012, his anemia recurred, and he was admitted to our hospital again. PSL 10–20 mg/day was restarted, and CyA 150 mg/day was added from April 2012. Increasing CyA and PSL dosage was difficult owing to toxic blood levels and exacerbation of diabetes, respectively. In December 2012, cyclophosphamide (CPA) 100 mg/day was

initiated for 21 days per month. Although the treatment with PSL, CyA, and CPA was useful, it failed to stabilize the hemolysis caused by cold exposure in the winter season.

In November 2013, rituximab therapy (375 mg/m^2 weekly for four weeks) was started on account of the predictable hemolysis in winter. The clinical course is shown in Fig.1. Physical examination did not reveal palpable lymphadenopathy and hepatosplenomegaly. Laboratory tests revealed the following: Hb 8.0 g/dL, Reti 2.2 %, Tbil 2.5 mg/dL, Dbil 0.8 mg/dL, LDH 280 IU/L, hemoglobin A1c 5.6 %, IgG 1004 mg/dL., IgA 127 mg/dL, IgM 89 mg/dL, complement components C3 121 mg/dL, C4 37 mg/dL, haptoglobin <10 mg/dL, and erythropoietin 113 mIU/mL. Results of a direct antiglobulin test were positive for complement components C3b and C3d (1+). Cold agglutinins of the IgM type had a titer of 1:1024. The results of tests for antinuclear, antimycoplasma, anti-rheumatoid factor, and anti-cyclic citrullinated peptide antibodies were negative. Bone marrow examination revealed erythroid hyperplasia and no evidence of lymphoproliferative diseases. Computed tomography did not reveal lymphadenopathy and hepatosplenomegaly. Before administration of rituximab, his Hb level was 8.0 g/dL and serum LDH level was 280 IU/L. Three months after the initial rituximab therapy (February 2014), his Hb level rose to 10.0 g/dL, and the LDH level dropped to reference levels (236 IU/L). His anemia and hemolysis findings improved. The results of the direct tests for antiglobin and cold agglutinin remained positive.

Table 1. *Laboratory data on December 2002*

White blood cell count	9500	/mm^3	Albumin	4.5	g/dl	Haptoglobin	<10	mg/dL
Red blood cell count	247×10^4	/mm^3	Total bilirubin	2.5	mg/dl	Direct antiglobulin test		
Hemoglobin	8.9	g/dl	Direct bilirubin	0.7	mg/dl	IgG	-	
Hematocrit	25	%	Aspartate aminotransferase	45	IU/l	Components C3b and C3d	2+	
Mean corpuscular volume	101.2	fl	Alanine aminotransferase	27	IU/l	Cold agglutinins of the IgM type titer	1:8192	
Mean corpuscular hemoglobin	36	pg	Lactate dehydrogenase (LDH)	1623	IU/l			
Mean corpuscular hemoglobin concentration	35.6	g/dl	Blood urea nitrogen	17.1	mg/dl	LDH isozyme		
Platelet count	51.3×10^4	/mm^3	Creatinine	1.1	mg/dl	LDH1	50.3	%
Reticulocyte	3	%	Uric acid	8.9	mg/dl	LDH2	34.8	%
			C-reactive protein	2.0	mg/dl	LDH3	9.9	%
			Immunoglobulin G (IgG)	1390	mg/dl	LDH4	3.2	%
			IgA	204	mg/dl	LDH5	1.8	%
			IgM	184	mg/dl			
			IgE	694	IU/ml			
			Soluble interleukin 2	499	U/ml			

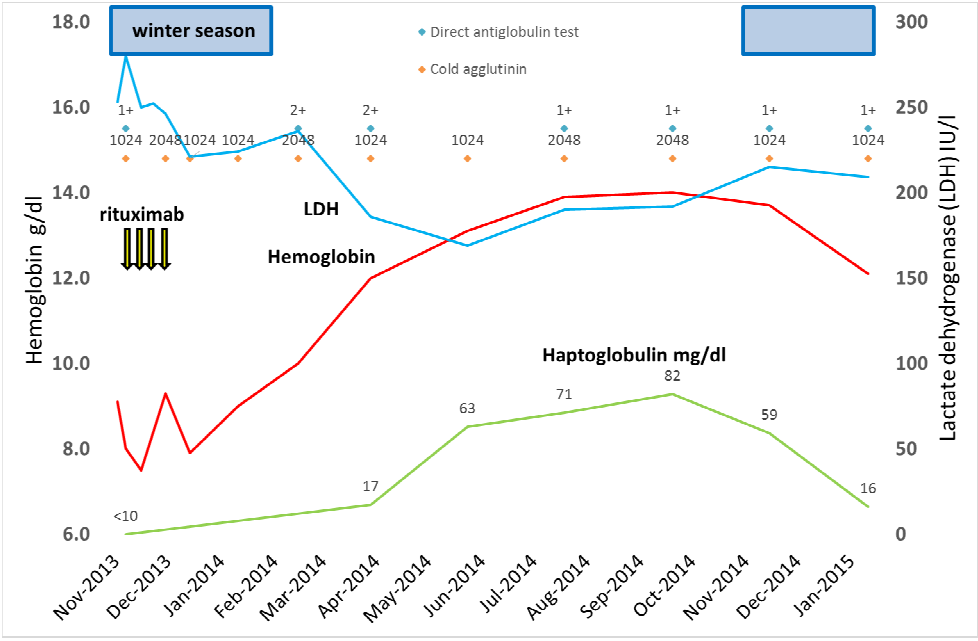

Figure 1. *Clinical course after administration of rituximab*

After administration of rituximab, his hemoglobin levels rose, and haptoglobin and LDH levels decreased, indicating improvement of the hemolysis.
Direct antiglobulin test: direct antiglobulin test positive for complement components C3b and C3d; Cold agglutinin: titer of cold agglutinins of IgM type

3. Discussion

B lymphocytes play a central role in humoral immunity. A dysfunction of B lymphocytes can result in autoimmune diseases, such as autoimmune hemolytic anemia. The pathological immune responses by B lymphocytes involve the production of autoantibodies, costimulation of T cells, antigen presentation, and secretion of cytokines. The treatment of autoimmune diseases with rituximab (anti-CD20 antibody), which suppresses B lymphocyte function, can result in clinical improvement [1].

Autoantibodies against erythrocytes cause autoimmune hemolytic anemia. This clinical condition is classified roughly by the antibody type into warm-AIHA and cold-AIHA [2]. Nevertheless, in some cases, the results of tests for a warm autoantibody and cold agglutinin are both positive, i.e. the condition called mixed AIHA. In the present case, mixed AIHA was diagnosed accordingly.

The effectiveness of rituximab against warm-AIHA has been reported previously. In one study [3], 27 patients with warm-AIHA received rituximab therapy. Overall, 25/27 (93 %) patients achieved an initial response to rituximab (8 complete responses and 17 partial responses). During the average follow-up of 20.9 months after rituximab treatment, five of the responders relapsed, three of whom were successfully retreated with rituximab.

The effectiveness of rituximab against cold-AIHA was also reported. In another study [4], 27 patients received rituximab therapy; 14 of 27 patients responded to the first course of rituximab, and 6 of 10 responded to retreatment. Overall, the response rate was 54 % (1 complete and 19 partial responses). Two non-responders and 3 patients who experienced relapse received second-line therapy with interferon-combined with a new course of rituximab, and 1 non-responder and 2 patients who experienced relapse achieved partial responses. Responders achieved a median increase in hemoglobin levels of 4 g/dL. Median time to response was 1.5 months, and median observed response duration was 11 months.

Only five case reports [5-9] showed the effectiveness of rituximab against mixed AIHA (Table.2). Before rituximab therapy, all these patients received other treatments. Just as in the present case, the patients in case 2, which is predominant hemolysis due to cold agglutinin, responded to rituximab therapy. In the present case, rituximab was administered in the winter season, and the hemolysis improved. Therefore, rituximab can be considered useful in the present case.

Table 2. *Case reports of mixed AIHA responsive to rituximab therapy*

case	age/sex	previous treatment	administration	reference
1	56/ female	corticosteroids, azathioprine, splenectomy	375mg/m^2 weekly for 4 weeks	5
2	71/ male	cyclophosphamide, prednisone	700 mg IV weekly for 4 weeks	6
3	40s/ female	corticosteroids, splenectomy	375mg/m^2 weekly for 4 weeks	7
4	62/ male	corticosteroids, plasmapheresis	375mg/m^2 weekly for 4 weeks	8
5	68/ female	corticosteroids	375mg/m^2 weekly for 4 weeks, 2 course	9

4. Conclusion

The present case suggests that rituximab is effective against mixed AIHA. Further studies are warranted to establish the effectiveness of rituximab against mixed AIHA.

Acknowledgement

We thank Tama-Hokubu Medical Center for permission to use rituximab in the present case.

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