International Journal of Clinical Medicine, 2015, 6, 496-499
Published Online July 2015 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2015.67066

An Evans Syndrome Case Expressing Anti-Jk^a Autoantibody under Condition of Primary IgA Immunodeficiency

Takeshi Sugimoto[1,2*], Ayumi Tani[2,3], Ikuyo Hayakawa[2], Makoto Hashimoto[2], Tomoko Yanai[4], Ikuko Kubokawa[4], Takeshi Mori[4], Takeshi Kato[4], Satoshi Hirase[4], Nobuyuki Yamamoto[4], Hironobu Minami[2], Akira Hayakawa[4]

[1]Department of Hematology and Oncology, Kita-Harima Medical Center, Ono, Japan
[2]Department of Blood Transfusion, Kobe University Hospital, Kobe, Japan
[3]Institute of Biomedical Research and Innovation, Kobe, Japan
[4]Department of Pediatric Medicine, Kobe University Hospital, Kobe, Japan
Email: [*]takeshi_sugimoto@kitahari-mc.jp

Received 24 June 2015; accepted 11 July 2015; published 16 July 2015

Abstract

Autoimmune haemolytic anaemia is a haemolytic disease resulting from an autoimmune reaction to the surface of red blood cells. A part of autoantibody is known to react with the blood type antigen. This is the case of a 14 years old female with Evans syndrome in which autoimmune haemolysis may cause from anti-Jk^a autoantibody reaction. As this case is complicated with primary IgA immunodeficiency syndrome, anti-Jk^a autoantibody may occur under the condition of primary immunodeficiency status, in which autoantibody production is accelerated. Considering the co-occurrence of autoimmune haemolytic anaemia and primary IgA immunodeficiency syndrome, analysis focusing on specificity for red blood cells antigens will be required in IgA immunodeficiency syndrome patients.

Keywords

Anti-Jk^a Autoantibody, Evans Syndrome, IgA Immunodeficiency

1. Introduction

Autoimmune haemolytic anaemia (AIHA) is a haemolytic disease resulting from an autoimmune reaction to the surface of red blood cells (RBCs). Haemolysis occurs when an autoantibody combines with an antigen on the

[*]Corresponding author.
How to cite this paper: Sugimoto, T., Tani, A., Hayakawa, I., Hashimoto, M., Yanai, T., Kubokawa, I., Mori, T., Kato, T., Hirase, S., Yamamoto, N., Minami, H. and Hayakawa, A. (2015) An Evans Syndrome Case Expressing Anti-Jk^a Autoantibody under Condition of Primary IgA Immunodeficiency. *International Journal of Clinical Medicine*, **6**, 496-499.
http://dx.doi.org/10.4236/ijcm.2015.67066

surface of RBCs, and the antigen-antibody reaction leads to RBCs destruction. The frequency of warm type AIHA (WAIHA), which is commonly observed, is estimated to be 40% - 70% of all AIHAs. In WAIHA, the mechanism producing the autoantibody for haemolysis has not been clearly elucidated. Immunoglobulin G (IgG) reacts with a RBCs antigen commonly in a panagglutinin pattern; however, some of the autoantibody reacts with the blood type antigen, *i.e.*, Rh blood type [1]. The patient presented here has Evans syndrome with primary IgA immunodeficiency syndrome (IgAD) in which haemolysis may be caused by anti-Jk^a autoantibody. The objective of this report is to accumulate cases possessing autoimmune specific RBCs antigen under the primary immunodeficiency status, in order to clarify antigen specificity.

2. Case Report

A 14-year-old female presented to the outpatient clinic of the Department of Paediatric Medicine, Kobe University Hospital, in July 2012 with the chief compliant of anaemia. In May 2011, she had presented with thrombocytopenia and a low titre of IgA, leading to a diagnosis of immune thrombocytopenic purpura (ITP) and IgA immunodeficiency. She had been initially treated with oral prednisolone (PSL) (1 mg/kg/day) for her ITP. Before arriving at our hospital, her PSL dose had been reduced without a recurrence of thrombocytopenia.

At the time of admission, she presented with generalized pallor, including anaemic conjunctiva. No purpura was observed, and no other abnormality was manifested. She had no history of pregnancy or receiving blood transfusions. The blood count test revealed the following: white blood cell count, 7.7×10^9/l; haemoglobin, 6.9 g/dl; hematocrit, 21.3%; reticulocytes, 9.8%; and platelet count, 349×10^9/μl, that was consistent with anaemia. Serological tests indicated some abnormality: LD, 250 IU/l; indirect bilirubin, 5.6 mg/dl; and haptoglobin, <10 mg/dl. Immunological tests confirmed primary IgAD that revealed a remarkable decrease of IgA, the level of which was <4 mg/dl (normal range, 110 - 410 mg/dl), with a normal range of other immunoglobulin subtypes. Complement titre (CH50) was decreased to 12.8 U/ml (normal, 30 - 45 U/ml) without C3 or C4 depression. Blood typing revealed type B and rhesus D positive (CCDee). Direct antiglobulin test (DAT) was positive, and monospecific DAT test with anti-IgG and anti-C3d anti-serum were both positive (anti-IgG, 2+; anti-C3d, 3+). Indirect antiglobulin test (IAT) was strongly positive for all panel blood cells. These results indicated that she had AIHA.

The antibody identification test using Panel Cell® (Ortho-Clinical Diagnostics) with polyethylene glycol (Immucor Inc.) and IAT method revealed a Jk(a)-specific reaction. IAT using the antibody-eluted sample from the patient's RBC by Gamma-Quin® (Immucor Inc.) had a non-specific positive reaction, whereas the IAT test using the 16-times diluted sample prepared from the original eluted sample was Jk(a)-specific phenotype with no other reaction. Therefore, the patient was diagnosed with AIHA with anti-Jk^a autoantibody. As her thrombocytopenia had been previously diagnosed as ITP, she was diagnosed with Evans syndrome (AIHA associated with immune thrombocytopenia). Immediately after her hospital admission in July 2012, the patient complained of dizziness, and her haemoglobin level decreased to 5.3 g/dl (**Figure 1**). She received two units of Jk(a) antigen- negative red blood cells with washing. Oral PSL therapy (1 mg/kg/day) was initiated. Her haemoglobin level transiently increased after red blood cells transfusion, whereas thrombocytopenia exacerbated after initiating PSL therapy. Haptoglobin increased to a normal level after PSL administration. Thrombocytopenia and haemolytic anaemia gradually improved by the end of August 2012. PSL treatment was reduced and stopped two months post-admission. However, the patient presented in December 2012 with thrombocytopenia without complicating anaemia; she received oral PSL therapy (1 mg/kg/day), leading to the improvement of thrombocytopenia. PSL treatment could be reduced by the normalization of platelet counts (**Figure 1**).

3. Discussion

This was an Evans syndrome case in which autoimmune haemolysis was caused by a Jk(a) antigen-antibody reaction. Since this patient had neither received a blood transfusion nor had a history of pregnancy before, we speculate that haemolysis may be caused by anti-Jk^a autoantibody. Among the autoantibodies able to cross-react with RBCs antigens, Rh type is the most popular [2]. Kidd group autoantibody, without being induced by drugs, is rarely recognized. Nine reports of haemolysis occurring due to anti-Jk^a autoantibody have been previously reported [3]-[11], of which three cases manifested as Evans syndrome [3] [5] [10] (**Table 1**).

Primary hypo-gammagulobulinemia, including IgAD, has the tendency to complicate autoimmune diseases

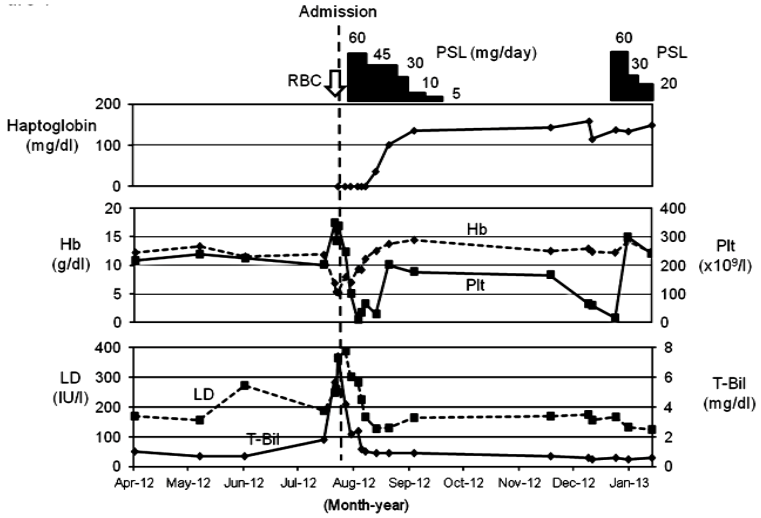

Figure 1. Clinical course. Abbreviations: Hb, haemoglobin; LD, lactate dehydrogenase; Plt, platelet count; PSL, prednisolone; RBC, red blood cells; T-Bil, total bilirubin.

Table 1. Summary of cases possessing Kidd blood group autoantibody.

	Age/ gender	Antigen	Hb (g/dl)	ITP (Evans)	Complicated disease at the diagnosis of AIHA	Medication	Author (year)
1	45/M	Jk^a	7	+	Neutropenia	PSL	Ciaffoni S [3] (1987)
2	0/F	Jk^a	5.2	−	Bacterial meningitis	RBC. PSL	Sander RP [4] (1987)
3	34/M	Jk^a	4.9	+	No complication	RBC, IVIG, Splenectomy, PSL, AZA, VCR	Ganly PS [5] (1988)
4	49/M	Jk^a	12	−	Lung cancer	−	Wernli RY [6] (1990)
5	38/F	Jk^a + Jk^b	7.5	−	Systemic lupus erythematosus	RBC, PSL	Grishaber JE [7] (1992)
6	60/M	Jk^a	6.3	−	Ulcerative colitis	RBC	Guastafierro S [8] (2004)
7	19/F	Jk^a	1.9	−	Systemic lupus erythematosus	PSL, IVIG	Wondergem MJ [9] (2006)
8	54/M	Jk^a	6.5	+	Common variable immunodeficiency	PSL, IVIG	Garcia-Munoz R [10] (2008)
9	5/F	Jk^a	4.1	−	Parvovirus B19 infection	Intravenous mPSL	Giovannetti G [11] (2013)
10	14/F	Jk^a	6.4	+	Selective IgA immunodeficiency	RBC, PSL	(Our case)

Abbreviations: AZA, Azathioprine; IVIG, Intravenous immunoglobulin; VCR, Vincristine; PSL, Prednisolone; mPSL, Methylprednisolone; RBC, Red blood cells; Jk^a, Jk^a autoantibody; Jk^b, Jk^b autoantibody; M, Male; F, Female.

[12]-[14]. Autoimmune haematological diseases, including ITP or AIHA, are most frequently observed in primary immunodeficiency diseases [15]. The diagnosis of IgAD occurs when IgA is <7 mg/dl with a concomitant normal level of IgG and IgM [15]. With regard to IgAD, the frequency of complicating AIHA or ITP was reported as 2% - 3% or 0.5%, respectively [12] [16]. In 10 AIHA cases caused by autoimmune Jk(a) antibody including ours, two cases were complicated primary immunodeficiency syndrome, *i.e.* one case of common variable immunodeficiency (CVID) [10] and our case of IgAD. In terms of autoimmune Jk(a) antibody, the frequency of carrying the background of immunodeficiency seems to be high. The reason for autoimmune disease, including AIHA from IgAD, is not conclusive; however, one hypothesis is that a dysfunction of SHP-1 tyrosine phosphate is related to the inhibitory immunoreceptor tyrosine-based activation motif in IgAD, resulting in hy-

per-activation of immune cells [16]. The evidence regarding the causative antigen in AIHA in primary immunodeficiency disease, including IgAD or CVID, is lacking. Considering the co-occurrence of AIHA and primary immune-deficient diseases, analysis focusing on specificity for RBC antigens will be required to perform adequate transfusion and understand autoimmune conditions.

4. Conclusion

Autoimmune haematological diseases, including ITP or AIHA, are most frequently observed in primary immunodeficiency diseases. Antigen analysis for autoimmune haemolysis will be considered under condition of primary IgAD.

Disclosure Statement

The authors declare no conflict of interest.

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