

Antibody against immunoglobulin E contained in blood components as causative factor for anaphylactic transfusion reactions

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BACKGROUND: Determining the mechanism underlying the development of transfusion reactions is important in transfusion therapy. Two bags of fresh-frozen plasma obtained from a donor (index donor) were implicated in two cases of anaphylactic transfusion reactions.

STUDY DESIGN AND METHODS: The serum prepared from the index donor plasma transfused into the second patient (Patient 2) was evaluated using cord blood–derived mast cells (CBMCs) incubated with Patient 2 plasma. The component in the serum required for the degranulation was determined and quantified by chromatography in combination with degranulation assay, Western blot analysis, and enzyme-linked immunosorbent assay. The component in the plasma required for CBMC sensitization was determined using human immunoglobulin (Ig)E or normal plasma in place of Patient 2 plasma in the assay. Sera collected from the index donor between 2001 and 2008 were examined for the CBMC degranulation factor.

RESULTS: The donor serum activated CBMCs incubated with Patient 2 plasma. The IgG fraction of the donor serum induced degranulation of CBMCs sensitized with IgE or plasma containing a normal IgE concentration. The IgG anti-IgE at a concentration higher than 2200 ng/mL, which showed CBMC degranulation activity, was detected in the donor sera for at least 7 years.

CONCLUSION: Transfusion of a high concentration of the anti-IgE in the donor plasma was suggested to induce mast cell degranulation in the patients leading to the development of anaphylactic transfusion reactions. Antibodies existing in not only the patient circulation but also the transfused blood might cause transfusion-induced anaphylaxis.

Transfusion reaction cases that occurred throughout Japan have been reported voluntarily to the Japanese Red Cross Society (JRCS) since 1993 to improve transfusion safety.¹ Among approximately 1500 cases of transfusion reactions reported each year, more than 200 cases have been classified as severe anaphylaxis, which is generally termed anaphylactic transfusion reactions.² JRCS has also been collecting patient serum or plasma samples as well as the remaining blood components implicated in transfusion reactions to analyze their adverse effects. However, the cause of the reactions remains unclear in most cases.

Mast cells are considered to play a key role in anaphylaxis.³ That is, the cross-linking of Fcε receptor I (FcεRI) via the complex of an antigen and immunoglobulin (Ig)E molecules on the cell surface stimulates the release of several enzymes and chemical mediators such as tryptase and histamine from the cells. These phenomena are closely related to the development of anaphylaxis and increased concentrations of serum or plasma tryptase are considered as a marker of anaphylaxis.^{4,5} The serum or plasma tryptase concentration in patients who developed anaphylactic transfusion reactions was observed to

ABBREVIATIONS: CBMC(s) = cord blood–derived mast cell(s); FcεRI = Fcε receptor I; hIgE = human immunoglobulin E from plasma; JRCS = Japanese Red Cross Society.

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increase significantly after the onset of the reactions, suggesting that mast cell degranulation is triggered during these transfusion reactions.⁶ We previously reported two cases of anaphylactic transfusion reactions associated with the transfusion of platelet (PLT) concentrates that contained oligomeric IgE capable of inducing the degranulation of cord blood–derived mast cells (CBMCs).⁷

JRCS was notified that another two bags of blood components obtained from a single donor were involved in two cases of anaphylactic transfusion reactions. In our preliminary analysis, the degranulation of CBMCs incubated with plasma from one of these patients upon stimulation with the serum sample prepared from one of the blood components was observed. In this study, we examined these samples by an *in vitro* degranulation assay using CBMCs and plasma protein purification techniques similar to those performed in a previous study.⁷ We propose a new mechanism by which the adverse reactions were elicited in these cases.

CASE REPORTS

Two cases of anaphylactic transfusion reactions involving two bags of fresh-frozen plasma (FFP) obtained from a donor were reported to JRCS.

Index donor

The index donor was a 64-year-old female in 2004. She donated more than 100 times between 1994 and 2008 and at least 18 bags of blood components including FFP prepared from her blood were transfused into recipients. Two of them were implicated in anaphylactic transfusion reactions that developed in two different patients described below. She had no history of allergy. The concentrations of IgE and IgG in her serum prepared from the FFP used for the second patient (Patient 2) were determined to be 24.2 ng/mL and 10.5 mg/mL, respectively, which were normal concentrations (lower than 415 ng/mL and 8.70–17.0 mg/mL,^{8,9} respectively). We examined retrospectively the hemovigilance data that had been accumulated in JRCS since 1993 by searching for reports concerning the blood component prepared from her blood. However, no cases were reported except these two cases of anaphylactic transfusion reactions. She had not donated since 2009 and currently she cannot donate owing to the age limitation for blood donation.

Patient 1

Patient 1 was a 53-year-old female suffering from pulmonary hypertension, renal failure, anemia, and thrombocytopenia. She had been diagnosed with thrombotic thrombocytopenic purpura and had been treated with plasma exchange four times without any transfusion reac-

tions. She had no history of allergy. She received her fifth plasma exchange using five sequential bags of FFP in 2004. Within 10 minutes after the start of transfusion of the fifth bag of FFP, which was donated by the index donor on April 17, 2004, her systolic blood pressure decreased from 136 to 30 mmHg, and her pulse rate also decreased to 30 beats/min; she then stopped breathing. She was considered to have developed anaphylactic transfusion reaction from her clinical manifestation.^{10,11} The IgE concentration in the pretransfusion plasma sample of the patient was 77.9 ng/mL. Her posttransfusion sample was not available for testing.

Patient 2

Patient 2 was a 62-year-old female with thrombotic thrombocytopenic purpura associated with systemic lupus erythematosus and underwent plasma exchange in 2005 using a bag of FFP obtained from the index donor on October 26, 2004. She had no history of allergy and she did not develop any adverse reactions during her transfusion therapies with four bags of FFP and a bag of PLT concentrate before the transfusion of FFP from the index donor. Ten minutes after the start of transfusion of FFP from the index donor, she started to feel throat pain and to wheeze, her forehead turned red, and her blood pressure dropped from 150/87 to 86/47 mmHg. Her oxygen saturation level measured by pulse oximetry was 86%. She was considered to have developed anaphylactic transfusion reaction from these clinical manifestations.^{10,11} Her plasma IgE concentration decreased from 177 ng/mL before the transfusion to 90.7 ng/mL after the transfusion. The tryptase concentration in her plasma increased from 4.0 to 20.5 µg/L (normal range in healthy individuals, 2.1–9.0 µg/L),¹² indicating mast cell activation.

MATERIALS AND METHODS

Plasma and serum

Plasma samples were collected from Patient 1 before the transfusion and from Patient 2 before and after the transfusion. An aliquot of plasma from the bag of FFP transfused into Patient 2 was incubated with 40 mmol/L CaCl₂ at 37°C for 2 hours and then at 4°C overnight to prepare serum. Seven serum samples were also collected from the index donor when she donated her blood between 2001 and 2008. Control samples were collected from healthy donors. All the samples were dialyzed against or buffer exchanged with saline for the degranulation assay. IgE and IgG concentrations in the samples were determined by peak-rate nephelometry using an immunochemistry system (IMMAGE 800, Beckman Coulter, Tokyo, Japan).

CBMCs

CBMCs, which are generally used for the *in vitro* study of mast cells,¹³ were prepared for degranulation assay.

Umbilical cord blood was obtained from the Japanese Red Cross Kanto-Koshinetsu Cord Blood Bank. Written informed consent was obtained from mothers for the use of the cord blood in transplantation- or transfusion-related studies in cases when the number of cord blood cells is not sufficient for transplantation. The differentiation of cord blood cells into mast cells was induced as previously described.⁷

CBMC degranulation assay

Mast cell degranulation activity in the test sample was determined from the percentage of tryptase or histamine release from activated CBMCs during the degranulation assay. CBMCs suspended in the culture medium were plated at 5×10^3 cells per well in a 96-well plate with 80 $\mu\text{g/mL}$ sodium heparin and 20% (vol/vol) of the pretransfusion plasma from Patient 2, four plasma samples from healthy donors, or the index donor serum in a final volume of 50 μL . The cells were then incubated at 37°C in 5% CO_2 for 6 hours. Subsequently, 60 μL of a sample solution containing the index donor serum or a healthy donor serum in 0.18% (wt/vol) dextrose, 2.6 mmol/L CaCl_2 , 1.8 mmol/L MgCl_2 , and 0.18% (wt/vol) bovine serum albumin was added to each well. After incubation at 37°C for 40 minutes, the supernatant of each well was collected. The tryptase and histamine concentrations in the supernatant were measured using an allergy and autoimmunity analyzer (UniCAP 100, Phadia, Tokyo, Japan) and a histamine enzyme immunoassay kit (A05890, Bertin Pharma, Yvelines, France), respectively. The percentage of tryptase or histamine release was calculated as described previously.⁷ To examine the effects of IgE and IgG on mast cell degranulation activity, CBMCs were incubated with 35.4 ng/mL human IgE from plasma (hIgE; 16-16-090705, Athens Research & Technology, Athens, GA) or human IgG from serum (hIgG; I4506, Sigma-Aldrich Japan, Tokyo, Japan). The CBMCs were then washed and incubated in a 96-well plate containing the sample solution described with or without 10,000 ng/mL hIgE or hIgG. The mast cell degranulation activity in the sample was then assessed.

Fractionation of index donor serum

To separate the components that induce CBMC degranulation from the other components of the serum, the index donor serum was fractionated by gel filtration and affinity chromatography. Gel filtration chromatography was carried out using 2 mL of the index donor serum on a column packed with prep grade (HR 16/50 and Superose 12, respectively, GE Healthcare Japan, Tokyo, Japan) at 4°C. The IgG fractions of the index donor serum and healthy donor serum were obtained using a protein G column (17-0404-01, GE Healthcare Japan) in accordance with the

manufacturer's protocol. The unbound fraction was collected as the pass-through fraction. Chromatographic fractions were assessed to determine mast cell degranulation activity using CBMCs sensitized with Patient 2 plasma and IgG concentration.

Detection of IgG anti-human IgE

In the Western blot analysis to detect the IgG anti-IgE, hIgE was blotted onto a transfer membrane (Immobilon-P, Nihon Millipore, Tokyo, Japan). The membrane was incubated with the index donor serum, healthy donor serum, or the IgG fraction of these sera, and then the IgG anti-IgE was detected using a horseradish peroxidase-conjugated anti-human IgG antibody (HRP-anti-IgG; 054220, Life Technologies Japan, Tokyo, Japan) and Western blotting detection reagents (ECL Plus, GE Healthcare Japan). hIgE on the membrane was visualized using a gold staining kit (Protogold, British BioCell International, Cardiff, UK). The IgG anti-IgE was quantified by enzyme-linked immunosorbent assay (ELISA). The test serum samples from the index donor or healthy donor were incubated in a 96-well plate (Nunc Immuno Plate PolySorp, Thermo Fisher Scientific, Kanagawa, Japan) coated with hIgE. The IgG anti-IgE in each well was detected using HRP-anti-IgG with 3,3',5,5'-tetramethylbenzidine (KPL, Gaithersburg, MD). A humanized monoclonal IgG anti-human IgE, omalizumab (Novartis Pharma, Tokyo, Japan), was used to generate a standard curve for quantification (detection range, 100-40,000 ng/mL).¹⁴

Statistical analysis

The percentage of tryptase release and the concentration of the IgG anti-IgE were determined in two and four independent experiments, respectively. The mean percentage of tryptase release was compared between samples by the two-tailed t test for independent samples using computer software (Excel 2010, Microsoft Corp., Redmond, WA). A p value of less than 0.05 was considered significant.

RESULTS

Index donor serum-induced degranulation of CBMCs sensitized with Patient 2 plasma

The index donor serum induced the degranulation of CBMCs incubated with Patient 2 plasma (Fig. 1). No significant difference was observed between the tryptase concentrations in the culture supernatants of CBMCs incubated with 20% (vol/vol) Patient 2 plasma only and in that incubated without it (data not shown). However, the CBMCs sensitized with Patient 2 plasma released tryptase when incubated with 2.5 to 40 μL of the index donor serum in 110 μL of assay solution in a dose-dependent manner; CBMCs incubated without Patient 2 plasma were

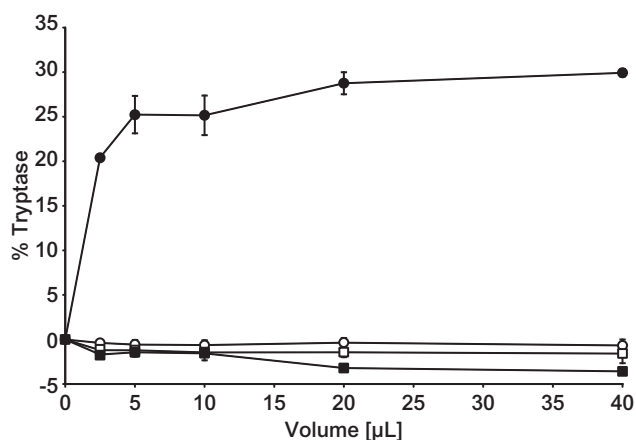


Fig. 1. Degranulation of CBMCs induced by index donor serum. CBMCs were incubated with (filled symbols) or without (open symbols) Patient 2 plasma followed by indicated volumes of index donor serum (●, ○) or healthy donor serum (■, □). The mean $\pm$ SD percentage of tryptase release is plotted.

not activated by the index donor serum. These results indicate that CBMCs were activated by the combination of Patient 2 plasma and the index donor serum.

CBMC degranulation induced by IgG fraction of index donor serum

Chromatographic fractionation was performed to separate the components of the index donor serum and identify those that activated CBMCs. Gel filtration fractions A37 to A49 induced the histamine release from CBMCs sensitized with Patient 2 plasma to a greater extent than the other fractions (Fig. 2A). These fractions contained a high concentration of IgG, suggesting that IgG is involved in the activation of CBMCs. The IgG fraction obtained from the index donor serum, as well as the index donor serum containing the same amount of IgG (3.56 μ L), induced the degranulation of CBMCs sensitized with Patient 2 plasma (Fig. 2B). Thus, it is considered that the factors in the index donor serum that activated Patient 2 plasma-sensitized CBMCs were in the IgG fraction.

Requirement of human IgE for CBMC sensitization

Next, the components in Patient 2 plasma required for CBMC sensitization were determined. CBMCs washed after incubation with Patient 2 plasma were activated by the index donor serum (data not shown). Hence, IgE may be necessary for CBMC sensitization because IgE binds to Fc ϵ RI on the CBMC surface and is not removed by washing.¹⁵ Indeed, CBMCs incubated with hIgE at the same concentration as that of IgE in Patient 2 plasma and then washed were activated by the index donor serum and the IgG fraction of the serum (Figs. 3A and 3B). Besides

Patient 2 plasma, other plasma samples could also sensitize CBMCs to the index donor serum (Fig. 3C). CBMCs incubated with plasma with an IgE concentration similar to that in Patient 2 plasma were activated by the index donor serum, whereas CBMCs incubated with plasma containing a low IgE concentration or an extremely high IgE concentration were not activated by the serum. These results suggest that normal IgE generally contained in human plasma could contribute as a factor for CBMC sensitization at suitable concentrations in place of Patient 2 plasma.

IgG anti-IgE in index donor serum activating IgE-sensitized CBMCs

As shown in Figure 3C, CBMCs were not activated by the index donor serum in the presence of a high IgE concentration. Moreover, CBMC degranulation induced by the IgG fraction of the index donor serum was inhibited by the addition of an excess amount of hIgE (Fig. 4A), suggesting that the IgG fraction recognized IgE. Western blot analysis revealed that IgG in the index donor serum bound to hIgE (Fig. 4B). Hence, it is considered that the index donor serum contained the IgG antibody against human IgE and this antibody triggered CBMC degranulation by the cross-linking of IgE-bound Fc ϵ RI on the cells.

IgG anti-IgE in index donor serum detected over 7 years

The IgG anti-IgE in the index donor serum samples collected between 2001 and 2008 was examined to determine the relationship between the presence of the antibody and the occurrence of anaphylactic transfusion reactions (Table 1). The IgG anti-IgE was detected in all eight samples by Western blot analysis. The concentration of the antibody was calculated to be in the range between 2200 and 8900 ng/mL by ELISA. All the test samples activated hIgE-sensitized CBMCs. These results indicate that the index donor had continuously produced the IgG anti-IgE over a long period of at least 7 years. CBMCs incubated with Patient 1 plasma were also degranulated after incubation with the index donor serum obtained from FFP that was from the blood donated on April 17, 2004, and that was transfused to Patient 1 (data not shown).

DISCUSSION

Mast cells in transfusion recipients are activated and degranulate during anaphylactic transfusion reactions,⁶ although the activation mechanism remains unclarified in most cases. In the cases presented in this study, the sera from the transfused FFP showed degranulation activity against CBMCs sensitized with the patient plasma and the

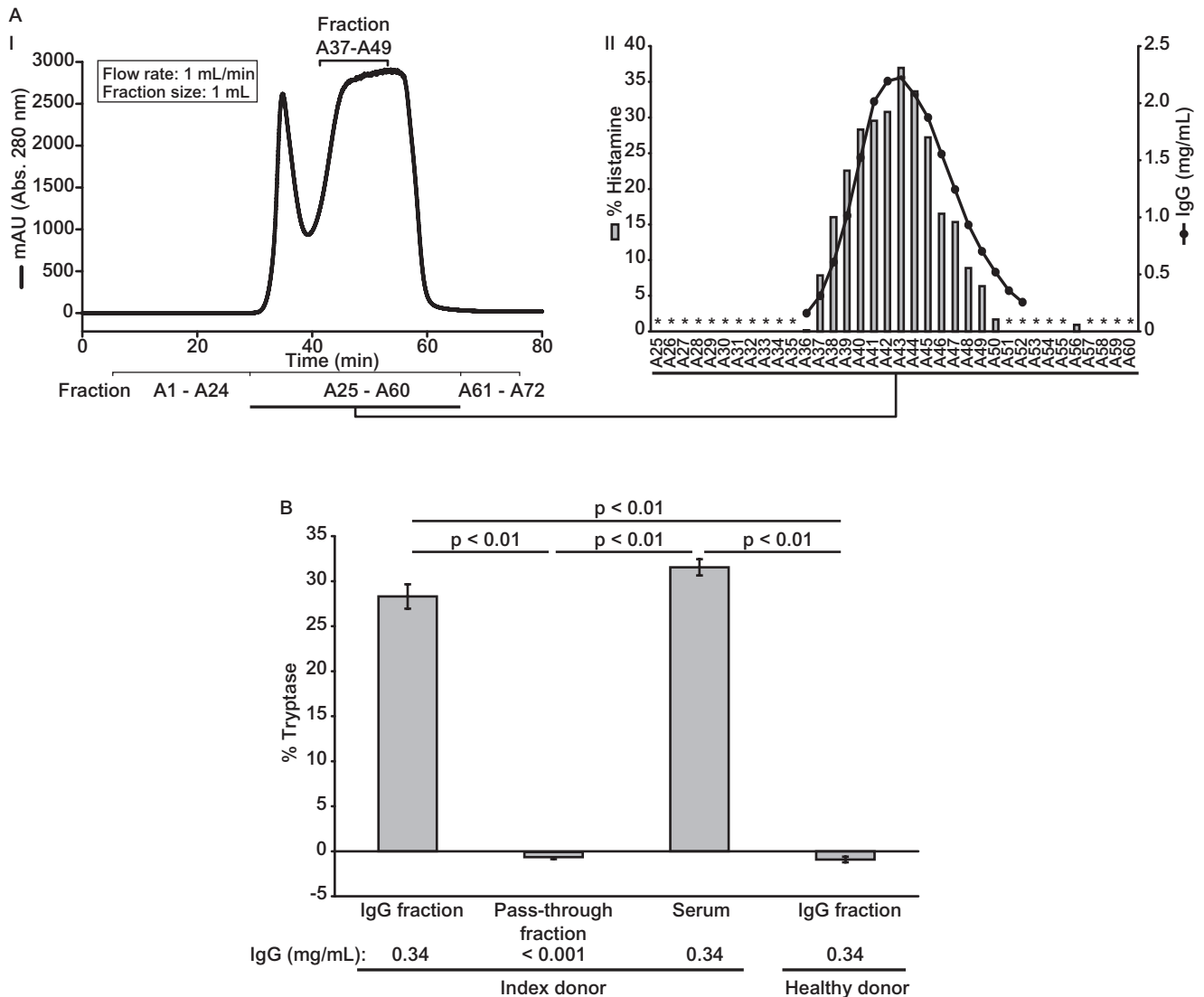


Fig. 2. Mast cell degranulation activity in fractions separated from index donor serum by chromatography. (A) The index donor serum was fractionated by gel filtration chromatography. (I) Chromatogram. (II) Elution patterns of mast cell degranulation activity and IgG. The histogram shows the percentage of histamine release during degranulation assay of 50 μ L of each fraction. *The percentage of histamine release was not higher than 0%. The solid line represents the IgG concentration in each fraction. (B) CBMC degranulation assay was performed using the indicated samples. The concentrations of IgG from the test samples in the assay solutions are indicated at the bottom of the panel. p values indicating significant differences are shown. The mean $\pm$ SD percentage of tryptase release is plotted.

factor responsible for CBMC degranulation was determined to be the IgG anti-human IgE in the donor plasma. It was suggested that the antibody was the causative factor for the anaphylaxis.

Autoantibodies against human IgE are found in patients with various diseases such as allergic disorders,^{14,16-19} systemic lupus erythematosus,²⁰ parasite infection,²¹ systemic sclerosis,²² Crohn's disease,²³ and visceral leishmaniasis.²⁴ The IgG anti-IgE was also detected in normal individuals in some studies.^{14,23} Generally, no more than 300 ng/mL IgG anti-IgE was observed in

patient serum samples.¹⁷⁻²² However, another report showed that the IgG anti-IgE concentrations in two of 96 individuals were more than 4000 ng/mL.¹⁴ The index donor was reported to have no history of allergic, autoimmune, or other diseases. Despite that, the IgG anti-IgE was detected in the index donor sera at relatively high concentrations ranging from 2200 to 8900 ng/mL. In our preliminary study to detect the IgG anti-IgE in approximately 250 serum samples prepared from the blood components, only one serum sample showed a high IgG anti-IgE concentration of 1200 ng/mL; however, that serum sample

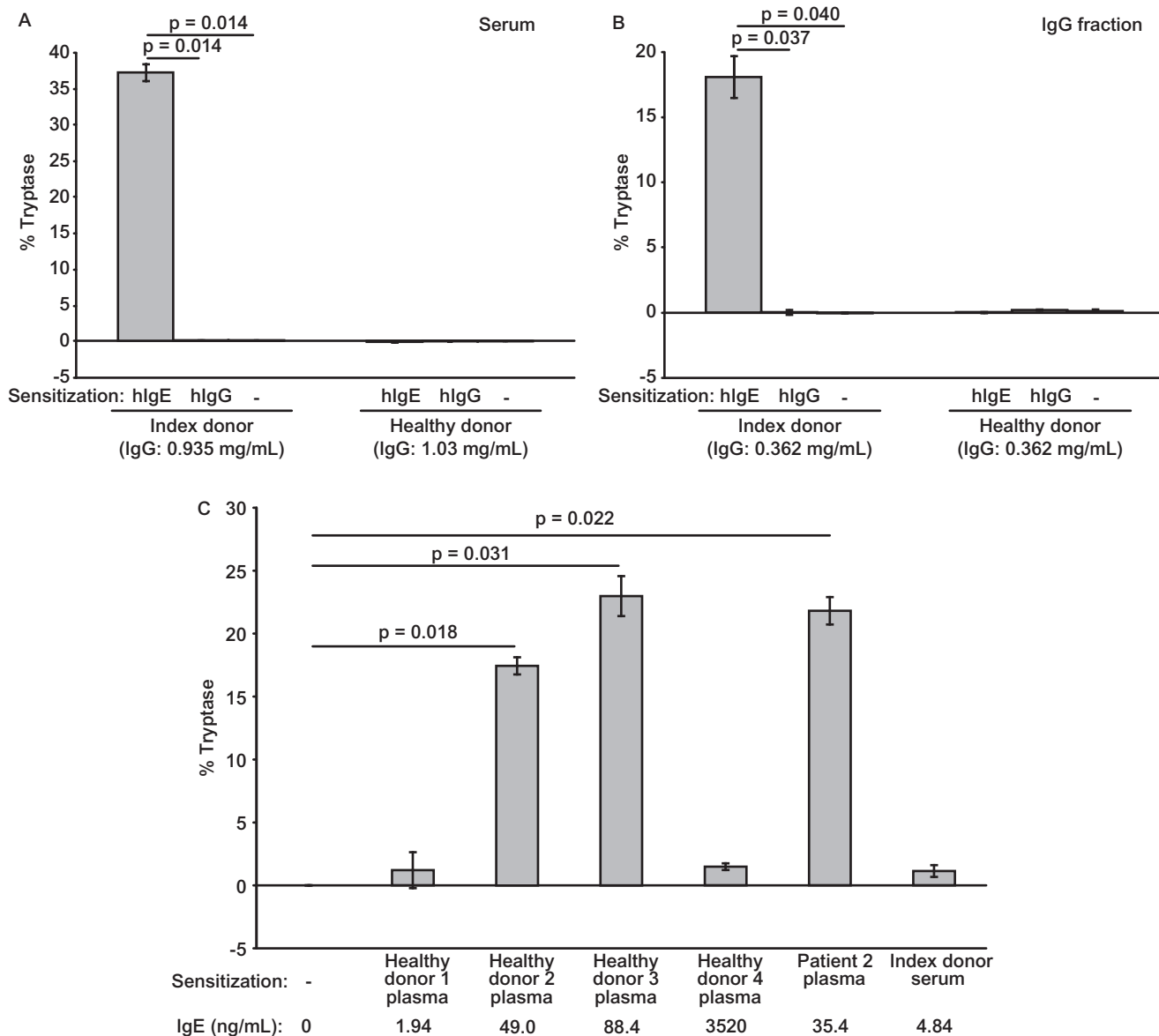


Fig. 3. Incubation of CBMCs for degranulation induced by index donor serum. CBMC degranulation assay was performed. (A and B) CBMCs incubated with 35.4 ng/mL hIgE or hIgG as the control were washed and then used for the degranulation assay of the indicated serum samples (A) and the IgG fractions of these samples (B). The IgG concentrations in the assay solutions are indicated at the bottom of the panel. (C) CBMCs were incubated with indicated plasma or serum, and then the degranulation assay was performed using 10 μ L of the index donor serum. The IgE concentrations at which CBMCs were incubated are indicated at the bottom of the panel. p values indicating significant differences are shown. The mean $\pm$ SD percentage of tryptase release is plotted.

did not activate IgE-sensitized CBMCs. Thus, it is suggested that the blood component with a high concentration of the IgG anti-IgE possessing mast cell degranulation activity similarly to the index donor plasma is very rare.

The concentration of IgE that sensitizes the cells seems to regulate whether CBMCs are induced to degranulate by the index donor serum. CBMCs were activated by the index donor serum when incubated with plasma containing appropriate IgE concentrations, as shown under Results, and when incubated with hIgE at

tens to a thousand of nanograms per milliliter but not at lower or higher than these concentrations (data not shown). The results suggest that at a low IgE concentration, the amount of IgE molecules on CBMCs was not sufficient to react with the IgG anti-IgE and that at an excessively high concentration of IgE, by forming an antigen-antibody complex, the IgE molecules in the assay solution inhibited the binding of the IgG anti-IgE to IgE on the CBMC surface to induce degranulation. Indeed, the IgE concentration in Patient 2 plasma decreased by half

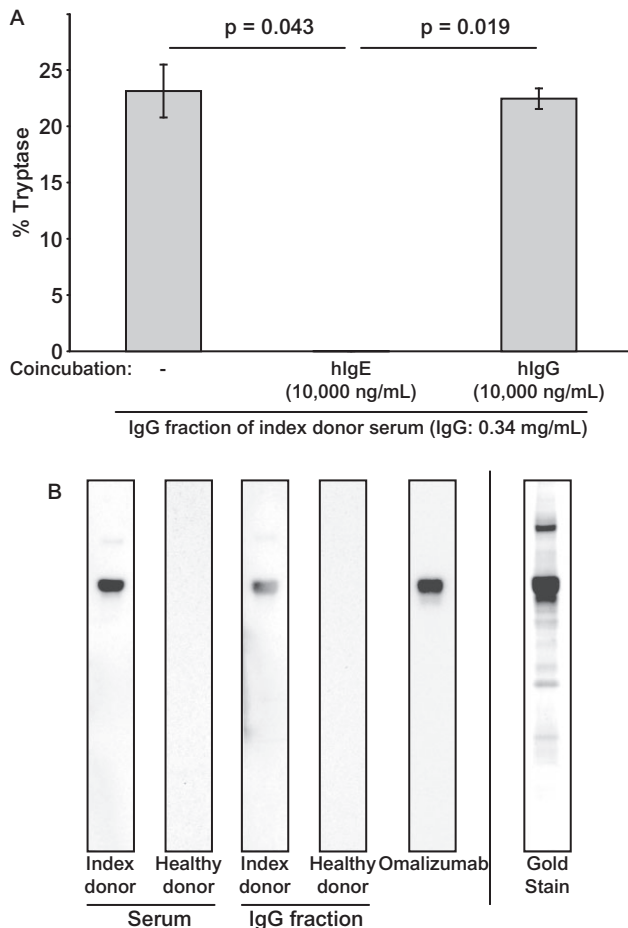


Fig. 4. Assessment of IgG anti-IgE in index donor serum activating IgE-sensitized CBMCs. (A) hIgE-sensitized CBMCs were washed and then used for the degranulation assay of the IgG fraction of the index donor serum (IgG: 0.34 mg/mL) coincubated with or without 10,000 ng/mL hIgE or with hIgG as the control. *p* values indicating significant differences are shown. The mean $\pm$ SD percentage of tryptase release is plotted. (B) The IgG antibody against IgE in the index donor serum was detected by Western blot analysis. The hIgE-blotted membrane was incubated with the samples indicated at the bottom of the panels.

after the occurrence of transfusion reactions. It might be suggested that the transfused IgG anti-IgE was consumed in part during its complexation with circulating IgE in the patient's blood.

In addition to the concentration of patient plasma IgE, a rapid transfusion rate might be required in the development of anaphylactic transfusion reactions. Both patients who developed anaphylactic transfusion reactions were treated by plasma exchange, in which the transfusion rate was considered to be much higher than that for supplementation of the blood coagulation factor. The rapid infusion of a high concentration of anti-IgE might facilitate the induction of the degranulation of the patients' mast cells. This may explain why no transfusion reaction cases other than the two cases presented in this study have been reported, despite the fact that many bags of blood components were prepared from the index donor blood.

In summary, the results suggest that the IgG anti-IgE in the transfused plasma caused anaphylactic transfusion reactions in these two patients. Thus, we propose a possible mechanism underlying these transfusion reactions. That is, the transferred antibody against a recipient's antigen causes anaphylactic transfusion reactions. An existing antibody in the patient blood that recognizes a substance in the transfused blood component has been proposed as a causative factor for anaphylactic transfusion reactions. However, concerning transfusion-related acute lung injury (TRALI), transferred antibodies, such as antibodies to human leukocyte antigens (HLA) and human neutrophil alloantigens (HNA) are considered as causative factors activating various cells in transfusion recipients.²⁵ The concentration of the transferred HLA antibody is suggested to be related to the development of TRALI.²⁶ Similarly, anaphylactic transfusion reactions could be induced in some patients in the presence of an adequate concentration of a transfused antibody against a specific antigen on the patient's cells, such as the IgG anti-IgE found in this study. Identification of causative antibodies in blood components would help reduce the risk of these transfusion reactions.

TABLE 1. IgG anti-IgE in index donor sera collected on various dates

Collection date	IgG anti-IgE				% Tryptase release†	
	Western blot analysis	Concentration*		SEM	Mean (%)	SD
		Mean (ng/mL)				
February 22, 2001	+	3200	210		30.7	2.0
August 23, 2002	+	3200	98		31.3	1.1
September 1, 2003	+	3000	230		30.8	2.4
April 17, 2004 (Case 1)	+	2300	130		23.3	2.1
September 17, 2004	+	2800	180		25.9	3.8
October 26, 2004 (Case 2)	+	2200	220		22.4	1.6
January 26, 2005	+	2500	250		21.1	3.0
July 11, 2008	+	8900	560		29.9	3.1

* The concentration of the IgG anti-IgE was measured by ELISA.

† For the degranulation assay, hIgE-sensitized CBMCs were activated with 10 μ L of each of the index donor sera collected on the indicated dates.

CONFLICT OF INTEREST

The authors report no conflicts of interest or funding sources.

REFERENCES

- Engelfriet CP, Reesink HW, Brand B, et al. Haemovigilance system. *Vox Sang* 1999;77:110-20.
- Momose S, Taira R, Muraoka M, et al. Haemovigilance data for five years by Japanese Red Cross Blood Service: transfusion-related adverse reactions and infections from 2004 to 2008 [abstract]. *Vox Sang* 2009;97(Suppl 1):165. XXth Regional Congress, Asia. 2009 Nov; Nagoya, Japan.
- Galli SJ, Tsai M. IgE and mast cells in allergic disease. *Nat Med* 2012;18:693-704.
- Schwartz LB, Yunginger JW, Miller J, et al. Time course of appearance and disappearance of human mast cell tryptase in the circulation after anaphylaxis. *J Clin Invest* 1989;83:1551-5.
- Enrique E, García-Ortega P, Sotorra O, et al. Usefulness of UniCAP-Tryptase fluoroimmunoassay in the diagnosis of anaphylaxis. *Allergy* 1999;54:602-6.
- Abe T, Mazda T, Watanabe Y, et al. Elevation of serum or plasma tryptase concentrations in patients with anaphylactic/oid shock [abstract]. *Vox Sang* 2009;97(Suppl 1):165-6. XXth Regional Congress, Asia. 2009 Nov; Nagoya, Japan.
- Abe T, Matsumoto C, Shimada E, et al. Immunoglobulin E oligomers identified in blood components activate mast cells: relevance to anaphylactic transfusion reaction. *Transfusion* 2011;51:2327-36.
- Shimazu S, Enomoto T. Serum IgE levels in healthy children [in Japanese]. *Allergol Immunol* 1995;2:920-5.
- Saito K, Kawai T, Ichihara K. Standards for ranges of 13 items of blood proteins among Japanese adults—results of a joint project of 7 organizations based on NCCLS Document C28-P and International Reference CRM470. 10. The results of the analysis conducted to set reference ranges for 13 [in Japanese]. *Rinsho Byori* 1996;101(Suppl):102-206.
- Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-7.
- Simons FE, Arduzzo LR, Bilò MB, et al., World Allergy Organization. World Allergy Organization guidelines for the assessment and management of anaphylaxis. *J Allergy Clin Immunol* 2011;127:593.e1-22.
- Hashimoto S, Sugawara N, Hata K, et al. Blood tryptase measured by “Uni-CAP Tryptase”; its basic and clinical evaluation [in Japanese]. *J Med* 2000;43:1161-65.
- Bischoff SC. Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. *Nat Rev Immunol* 2007;7:93-104.
- Eckman JA, Hamilton RG, Gober LM, et al. Basophil phenotypes in chronic idiopathic urticaria in relation to disease activity and autoantibodies. *J Invest Dermatol* 2008;128:1956-63.
- Saito H, Ebisawa M, Tachimoto H, et al. Selective growth of human mast cells induced by *Steel* factor, IL-6, and prostaglandin E₂ from cord blood mononuclear cells. *J Immunol* 1996;157:343-50.
- Smith SJ, Jones NS, Shakib F. The prevalence of IgG1 and IgG4 autoantibodies to IgE in patients with allergic and non-allergic rhinitis. *Clin Otolaryngol Allied Sci* 1995;20:540-3.
- Nawata Y, Koike T, Yanagisawa T, et al. Anti-IgE autoantibody in patients with bronchial asthma. *Clin Exp Immunol* 1984;58:348-56.
- Nawata Y, Koike T, Hosokawa H, et al. Anti-IgE autoantibody in patients with atopic dermatitis. *J Immunol* 1985;135:478-82.
- Gruber BL, Baeza ML, Marchese MJ, et al. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988;90:213-7.
- Gruber BL, Kaufman LD, Marchese MJ, et al. Anti-IgE autoantibodies in systemic lupus erythematosus. Prevalence and biologic activity. *Arthritis Rheum* 1988;31:1000-6.
- Nawata Y, Koike T, Tsutsumi A, et al. Anti-IgE autoantibody in patients with parasite infection [in Japanese]. *Arerugi* 1988;37:204-7.
- Kaufman LD, Gruber BL, Marchese MJ, et al. Anti-IgE autoantibodies in systemic sclerosis (scleroderma). *Ann Rheum Dis* 1989;48:201-5.
- Huber A, Genser D, Spitzauer S, et al. IgE/anti-IgE immune complexes in sera from patients with Crohn’s disease do not contain food-specific IgE. *Int Arch Allergy Immunol* 1998;115:67-72.
- Atta AM, Sousa-Atta ML, D’Oliveira A, et al. IgG anti-IgE autoantibodies in visceral leishmaniasis. *Mem Inst Oswaldo Cruz* 2002;97:101-3.
- Bux J. Antibody-mediated (immune) transfusion-related acute lung injury. *Vox Sang* 2011;100:122-8.
- Hashimoto S, Nakajima F, Kamada H, et al. Relationship of donor HLA antibody strength to the development of transfusion-related acute lung injury. *Transfusion* 2010;50:2582-91. ■