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Brief Communication

Serum MRGPRX2 as a Long-term Biomarker for Iodinated Contrast Media-Induced Anaphylaxis

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ABSTRACT

The diagnosis of anaphylaxis is based on the clinical history. The utility of tryptase measurements in clinical setting is limited. Mas-related G protein-coupled receptor-X2 (MRGPRX2) is expressed in mast cells and is involved in the degranulation of these cells. We evaluated the potential of MRGPRX2 as a diagnostic biomarker in patients with iodinated contrast media (ICM)-induced immediate hypersensitivity reactions (IHRs). A total of 173 patients with documented ICM-induced IHR within 4 months from registration were enrolled and skin tests for the culprit ICM were performed. The time interval was evaluated as the duration between the onset of ICM-induced IHR and the measurement of serum MRGPRX2 levels. Serum MRGPRX2 concentration was determined using an enzyme-linked immunosorbent assay kit. Of the 173 patients, 33 and 140 were included in the anaphylaxis and non-anaphylaxis groups, respectively. Serum MRGPRX2 levels were significantly higher in the anaphylaxis than in the non-anaphylaxis group (29.9 ± 24.1 vs. 20.7±17.5, $P = 0.044$). Serum MRGPRX2 showed a moderate predictive ability for anaphylaxis, with an area under

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the curve of 0.61 (P = 0.058). When groups were classified based on the time interval, T1(0-2months) and T2 (2-4months), patients with anaphylaxis had higher MRGPRX2 levels compared to the non-anaphylaxis group in the T2 group (36.5±19.2 vs. 20.5±19.0, P = 0.035). This pilot study shows that serum MRGPRX2 is a potential long-term biomarker for predicting anaphylaxis, particularly ICM-induced anaphylaxis. Further studies are needed to determine the role of MRGPRX2 in anaphylaxis in a larger population of patients with various drug-induced IHRs.

Keywords: Hypersensitivity; drug; anaphylaxis; tryptase

INTRODUCTION

Adverse drug reactions are major clinical problems. Among these, immediate hypersensitivity reactions (IHRs) to iodinated contrast media (ICM) are an important clinical problem, given the increasing number of administrations per year worldwide.[1] The clinical presentation ranges from mild urticaria to severe anaphylaxis or even death in 1 per 100,000 administrations.[2]

Anaphylaxis is a potentially fatal systemic adverse drug reaction. It is an unpredictable and mostly dose-independent event that occurs suddenly after exposure to the causative drug.[3,4] Anaphylaxis is diagnosed based on clinical history, leading to occasional misdiagnosis. Serum tryptase is useful to support anaphylaxis showing elevated levels. Serum acute tryptase paired with a serum baseline tryptase is performed to confirm a mast cell mediated anaphylactic event and rule out systemic mastocytosis.[5] However, tryptase has a short half-life; hence, blood samples should be obtained within 30 minutes–2 hours after anaphylaxis.[5,6] This limits the utility of tryptase measurements in clinical settings.

Mas-related G protein-coupled receptor-X2 (MRGPRX2), which is expressed on mast cells (MCs), is involved in the degranulation of these cells in the immunoglobulin E (IgE)-independent pathway of anaphylaxis.[7] MRGPRX2 may be a receptor for many drugs and cationic proteins that are capable of inducing direct MC degranulation and anaphylactic events.[8] This study aimed to evaluate serum MRGPRX2 levels in patients with ICM-induced IHR and determine their usefulness as a potential biomarker of anaphylaxis.

MATERIALS AND METHODS

Study subjects

We studied 173 patients with documented ICM-induced IHR within 4 months of registration at 14 medical centers in Korea between January 2018 and December 2020. The inclusion criteria were age ≥ 19 years and ICM-induced IHR determined by an allergist. Patients were excluded if the causal factors for IHR were ambiguous or if other relevant causes were combined. IHR was defined as an adverse reaction with onset during infusion or within 1 hour of its completion, with features suggestive of MC degranulation.[1] If cases met the World Allergy Organization (WAO) consensus clinical definitions,[9] they were classified into the anaphylaxis group. This study was approved by the Institutional Review Boards and Ethics Committees of all centers of interest, and the subjects provided written informed consent (IRB No. 2018-0797).

Assessment of IHR to ICM

IHR severity was classified into 3 categories according to the guidelines of the ACR Manual on Contrast Media.[10] The mild reaction was self-limiting, with signs and symptoms showing no evidence of progression, including simple rashes, coughing, hives, or swelling of the eyes and face. Moderate reactions had more pronounced symptoms, including laryngeal edema, bronchospasm, or generalized erythema. Severe reactions were life-threatening and included severe laryngeal edema, profound hypotension, convulsions, unresponsiveness, or cardiopulmonary arrest.

Skin tests with suspected causal ICM were performed at least 2 weeks after IHR to decrease the possibility of false-negative results. This skin tests of ICM have already been validated in previous study.[11] Patients with positive and negative skin test results for the culprit ICM were classified into IgE- and non-IgE-mediated IHR groups, respectively. Skin tests were conducted as follows. For the positive control, a prick test with a solution of histamine hydrochloride (10 mg/mL) was used, whereas for the negative control a physiological saline solution was used. For intradermal tests (IDT) of the culprit ICM, a 1/10 dilution of 7 ICMs was used in this study as follows: 1) iopromide (Ultravist; Bayer Healthcare, Brussels, Belgium), 2) iohexol (Omnipaque; GE Healthcare, Chicago, IL, USA), 3) iopamidol (Pamiray; Dongkook Pharm Co., Ltd, Seoul. Korea), 4) ioversol (Optiray; Mallinckrodt PLC, St. Louis, MO, USA), 5) iobitridol (Xenetics; Guerbet, Gorinchem, Netherlands), 6) iomeprol (Iomeron; Bracco, Milano, Italy), and 7) iodixanol (Visipaque; GE Healthcare). Each test was read 15 minutes after administration. The prick test result was considered positive when the cutaneous response was a wheal of at least 3 mm with surrounding flare, whereas the IDT result was considered positive with a wheal of at least 5 mm with surrounding flare.[12]

Assessment of time interval

We assessed the time interval between the occurrence of ICM-induced IHR and registration, as these 2 time points varied. At the time of registration, serum MRGPRX2 levels were measured in all patients. The time interval for each patient was defined as the duration between the occurrence of ICM-induced IHR and MRGPRX2 level measurement (**Fig. 1**). Patients were divided into 2 groups: the T1 group, comprising patients who had a time interval of 0–2 months, and the T2 group, comprising patients who had a time interval of 2–4 months.

Measurement of serum MRGPRX2 levels

Serum MRGPRX2 concentrations were determined using a commercially available quantitative sandwich enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, San Diego, CA, USA), following the manufacturer's instructions. Serum MRGPRX2 levels were

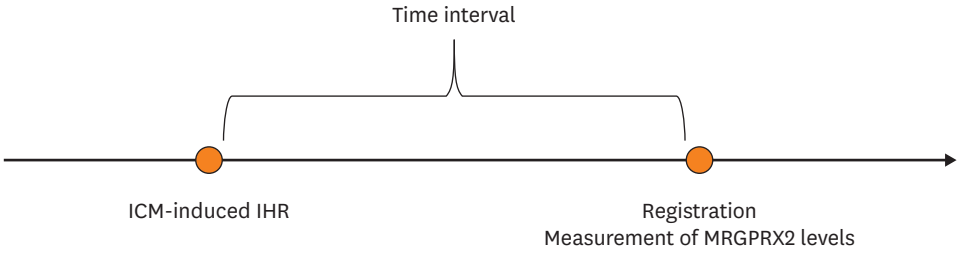

Fig. 1. Definition of time interval. The time interval was defined as the duration between ICM-induced IHR occurrence and serum MRGPRX2 level measurement at registration.
ICM, iodinated contrast media; IHR, immediate hypersensitivity reaction; MRGPRX2, Mas-related G protein-coupled receptor-X2.

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measured at a single center, Asan Medical Center, using serum samples received from each institution. The results are expressed in ng/mL. This ELISA detected human MRGPRX2 with a minimum detection limit of 3.12 ng/mL and a maximum detection limit of 100 ng/mL with an estimated sensitivity of 1.0 ng/mL.

Statistical analysis

Student's *t*-test, Welch's *t*-test, and Wilcoxon rank-sum test were used to determine the between-group differences in continuous variables. Pearson's χ^2 test and Fisher's exact test were used to analyze categorical variables. The diagnostic performance of MRGPRX2 in predicting anaphylaxis was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). All calculations were performed using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) statistical software. $P < 0.05$ was considered significant.

RESULTS

Clinical characteristics of study subjects

The baseline characteristics of 173 patients with ICM-induced IHR are summarized in **Table 1**. Mean age (± standard deviation) was 54 ± 13.1 years and women were predominant (61.6%). A total of 9.8% and 4.6% of the patients had allergic rhinitis and asthma, respectively. According to the severity assessment, patients in the severe group (47.4%) were more frequent than those in the mild and moderate groups (28.3% and 24.3%, respectively).

The patients were classified into 2 groups according to anaphylaxis: anaphylaxis (n = 33) and non-anaphylaxis (n = 140) groups (**Table 2**). There were no statistically significant differences in age, sex, body mass index, of medical history such as allergic rhinitis and asthma between the anaphylaxis and non-anaphylaxis groups. In addition, no differences were observed in total IgE levels or blood absolute eosinophil counts. The prevalence of IgE-mediated type was higher in the anaphylaxis group than in the non-anaphylaxis group (63.6% vs. 37.1%, $P = 0.006$).

Differences in serum MRGPRX2 levels related to anaphylaxis

Serum MRGPRX2 levels were significantly higher in the anaphylaxis group than in the non-anaphylaxis group (29.9 ± 24.1 vs. 20.7±17.5, $P = 0.044$; **Table 2**, **Fig. 2A**). Serum MRGPRX2 levels were not significantly different among the mild, moderate, and severe groups (19.3±16.0 vs. 22.6±16.9 vs. 24.1±21.9, $P = 0.411$; **Supplementary Fig. S1A**). A total of 162 patients underwent skin tests, 73 patients with positive results were classified into the IgE-mediated group and 89 patients with negative results were classified into the non-IgE-

Table 1. Baseline characteristics of the study participants

Characteristics	Study subjects (n = 173)
Age (yr)	54.0 ± 13.1
Female	106 (61.6)
BMI (kg/m^2)	24.3 ± 4.2
Allergic rhinitis	17 (9.8)
Allergic asthma	8 (4.6)
Severity	
Mild	49 (28.3)
Moderate	42 (24.3)
Severe	82 (47.4)

Values are presented as mean ± standard deviations or number (%).
BMI, body mass index.

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Table 2. Comparison of the clinical characteristics between the anaphylaxis and non-anaphylaxis groups

Characteristics	Anaphylaxis (n = 33)	Non-anaphylaxis (n = 140)	*P* value
Age (yr)	57.9 ± 12.6	53.1 ± 13.1	0.059
Female	16 (48.5)	90 (64.7)	0.084
BMI (kg/m^2)	24.8 ± 4.1	24.2 ± 4.3	0.469
Allergic rhinitis	2 (6.1)	15 (10.7)	0.533
Allergic asthma	3 (9.1)	5 (3.6)	0.179
IHR type*			0.006
IgE-mediated	21 (63.6)	52 (37.1)	
Non-IgE-mediated	12 (36.4)	88 (62.9)	
Total IgE (kU/L)†	16.1 ± NA	372.7 ± 368.0	NA
Blood eosinophil, absolute count (/uL)	116.4 ± 87.9	159.8 ± 213.9	0.93
MRGPRX2 (ng/mL)	29.9 ± 24.1	20.7 ± 17.5	0.044

Values are presented as mean ± standard deviation or number (%).
BMI, body mass index; IHR, immediate hypersensitivity reaction; IgE, immunoglobulin E; NA, not applicable.
*IHR type was confirmed by skin test reactivity of the culprit iodinated contrast medium. Patients with a positive response to the skin test were classified into the IgE-mediated-type group.
†The total number of patients with IgE level is 14 (1 with anaphylaxis, 13 with non-anaphylaxis). Inter-group comparative analysis is not feasible.

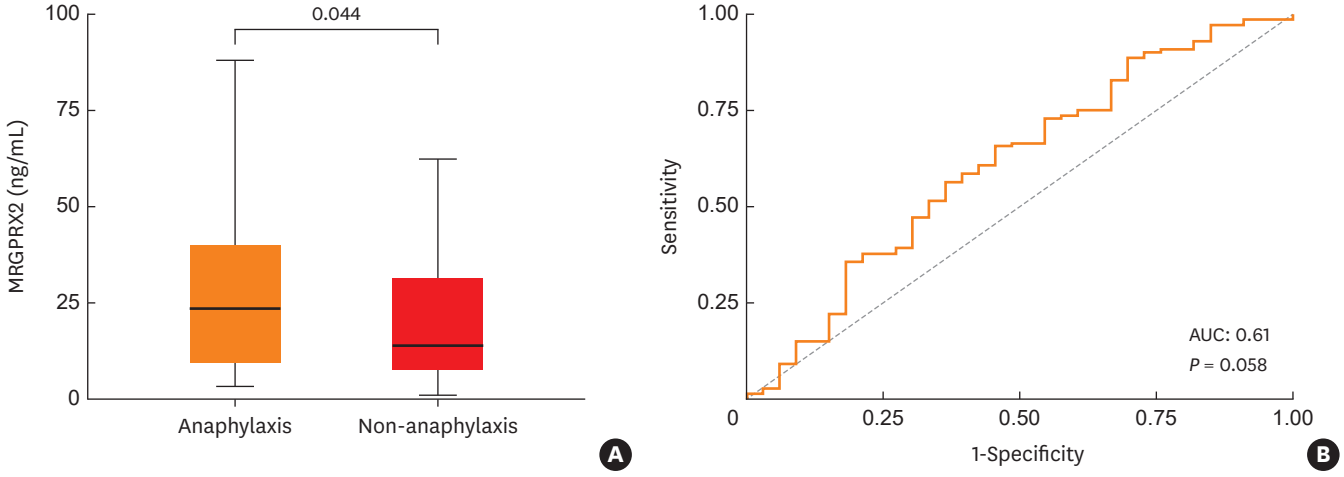

Fig. 2. Differences in serum MRGPRX2 levels related to anaphylaxis. (A) Serum MRGPRX2 levels were significantly higher in the anaphylaxis group than in the non-anaphylaxis group (29.9 ± 24.1 vs. 20.7 ± 17.5, *P* = 0.044). (B) The AUC of serum MRGPRX2 for predicting anaphylaxis was 0.61 (*P* = 0.058) and the cut-off value was 22.3 ng/mL.
MRGPRX2, Mas-related G protein-coupled receptor-X2; AUC, area under the curve.

mediated group. Serum MRGPRX2 levels did not differ significantly between the 2 groups (22.7±18.7 vs. 22.2±19.8, *P* = 0.874; **Supplementary Fig. S1B**).

In the ROC analysis for predicting anaphylaxis, the AUC of serum MRGPRX2 was 0.61, with 65.7% sensitivity and 54.5% specificity (*P* = 0.058; **Fig. 2B**). The optimal serum MRGPRX2 cutoff value for determining anaphylaxis was 22.3 ng/mL.

Differences in serum MRGPRX2 levels related to the time interval

Serum MRGPRX2 levels were higher in the anaphylaxis group than in the non-anaphylaxis group at T1 and T2 (**Table 3**, **Fig. 3**). Patients with anaphylaxis had significantly higher serum MRGPRX2 levels than those in the non-anaphylaxis group in T2 (36.5 ± 19.2 vs. 20.5 ± 19.0, *P* = 0.035); however, there were no significant differences between the 2 groups in the T1 interval.

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Table 3. Serum MRGPRX2 levels according to time interval from ICM-induced IHR

Time interval	Anaphylaxis (n = 33)	Non-anaphylaxis (n = 140)	*P* value
T1 (0–2 months)			0.287
No. of patients	26	93	
MRGPRX2 (ng/mL)	28.15 ± 25.32	20.77 ± 16.83	
T2 (2–4 months)			0.035
No. of patients	7	47	
MRGPRX2 (ng/mL)	36.53 ± 19.19	20.45 ± 18.98	

MRGPRX2, Mas-related G protein-coupled receptor-X2; ICM, iodinated contrast media; IHR, immediate hypersensitivity reaction

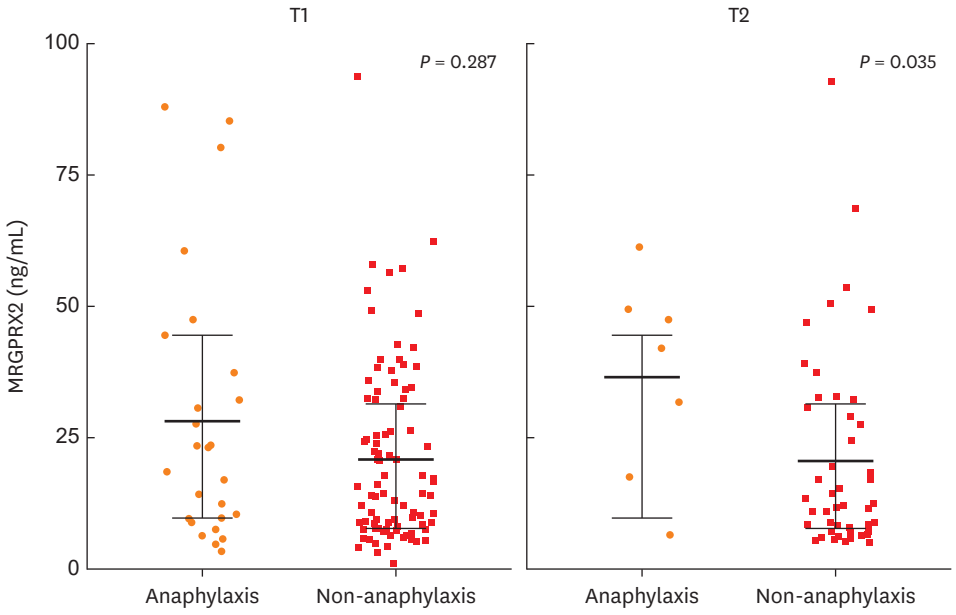

Fig. 3. Differences in serum MRGPRX2 levels related to time intervals. The T1 group comprised patients who had a time interval of 0–2 months, and the T2 group comprised patients who had a time interval of 2–4 months. Patients with anaphylaxis had significantly higher MRGPRX2 levels than those in the non-anaphylaxis group in T2 (36.53 ± 19.19 vs. 20.45 ± 18.98, *P* = 0.035).
MRGPRX2, Mas-related G protein-coupled receptor-X2.

DISCUSSION

We made the following observations in this study: 1) serum MRGPRX2 levels were significantly higher in the anaphylaxis group than in the non-anaphylaxis group; 2) serum MRGPRX2 levels may be a predictor for determining anaphylaxis; and 3) serum MRGPRX2 levels were detectable at a high concentration for 4 months from the onset of anaphylaxis. Overall, this study showed that serum MRGPRX2 level is a potential long-term biomarker for predicting ICM-induced anaphylaxis.

To the best of our knowledge, this is the study to assess serum MRGPRX2 levels as a biomarker of anaphylaxis in patients with ICM-induced IHR. Anaphylaxis is a severe and potentially life-threatening allergic reaction that requires prompt recognition and immediate medical intervention.[13] Given that anaphylaxis remains a clinical diagnosis, there is a need for biomarkers to confirm anaphylaxis.[14] This study highlighted the potential of serum MRGPRX2 as a biomarker, along with tryptase, for supporting the diagnosis of anaphylaxis. Serum MGPRX2 levels were elevated in patients with anaphylaxis compared to those in the non-anaphylaxis group. Unfortunately, the AUC results in the ROC analysis were not

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significantly superior, potentially because of the limited number of patients with anaphylaxis included in this study.

Although elevated tryptase levels are commonly used as a diagnostic biomarker, they may not always be elevated in all cases of anaphylaxis, particularly in non-IgE-mediated reactions.[15] MRGPRX2, one of the G protein-coupled receptors expressed in MCs, is involved in IgE-independent anaphylaxis.[7] Some drugs, such as neuromuscular blockers, quinolones, and opioids, have non-IgE-mediated reactions that bind directly to MRGPRX2, triggering MCs and basophil degranulation.[16] It was anticipated that serum MRGPRX2 levels would be higher in non-IgE mediated anaphylaxis compared to IgE-mediated anaphylaxis. However, no significant differences were observed between the two groups in this study. This may result from the existence of various non-MC/basophil pathways in non-IgE mediated anaphylaxis mechanisms, such as IgG-neutrophil/macrophage-mediated and complement activation-mediated anaphylaxis.[17-19]

The limitation of using tryptase levels for the diagnosis of anaphylaxis is the timing of blood sampling. Blood samples for tryptase measurements should be obtained within the half-life of tryptase (2 hours) because it is primarily released from MCs and reaches its peak within 1–2 hours.[20] The elevation in serum tryptase greater than (2 + [1.2 × baseline tryptase level]) indicates the involvement and activation of MCs.[21] In this study, the major advantage of serum MRGPRX2 was its ability to sustain detection for a longer duration compared to tryptase in patients with anaphylaxis. The exact mechanism underlying this result is unknown because the precise role of MRGPRX2 in MCs and its validated endogenous ligands remain unclear.[22] Further studies are needed to elucidate the signaling mechanisms of MRGPRX2 in drug-induced IHRs.

This study had several limitations. First, we measured serum MRGPRX2 levels at registration and lacked data on baseline and serial changes in serum MRGPRX2 concentrations in the same patient. Secondly, serum MRGPRX2 and tryptase levels were not directly compared because there were no data regarding the tryptase levels. Thirdly, a suboptimal AUC value in ROC analysis was observed, possibly due to more frequent IgE-mediated reactions compared to non-IgE-mediated reactions in the anaphylaxis group. Fourthly, there was no healthy control group. Fifthly, this study included a modest number of participants, and unknown confounding factors were not considered. Finally, the drugs used in this analysis were limited to ICMs. Further studies involving larger samples of patients with various drug-induced IHRs are required to validate the role of serum MRGPRX2 levels in anaphylaxis, particularly in relation to the severity and type of IHR (IgE-dependent and IgE-independent pathways).

In conclusion, serum MRGPRX2 levels are a promising biomarker for the diagnosis of ICM-induced anaphylaxis. A valuable advantage of using serum MRGPRX2 as a biomarker of anaphylaxis is that it can be measured over a longer period without sampling time constraints. The role of serum MRGPRX2 in anaphylaxis requires further studies in a larger population with various drug-induced IHRs.

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SUPPLEMENTARY MATERIAL

Supplementary Fig. S1

(A) Serum MRGPRX2 levels according to severity were not significantly different among mild, moderate, and severe groups (19.3 ± 16.0 vs. 22.6 ± 16.9 vs. 24.1 ± 21.9, $P = 0.411$). (B) Serum MRGPRX2 levels did not differ significantly between the IgE-mediated and non-IgE-mediated groups (22.7 ± 18.7 vs. 22.2 ± 19.8, $P = 0.874$).

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