

Fatal anaphylaxis caused by gadolinium due to beta-tryptase–induced hemorrhagic diathesis



Alicia Prieto-García, MD, PhD^a,
Esther Pérez-David, MD, PhD^b, Carolina Devesa, MD^b,
Pilar Tornero, MD^a, Lawrence B. Schwartz, MD, PhD^c,
Cristina Pascual, MD, PhD^d, and
Mariana C. Castells, MD, PhD^e

Clinical Implications

- We report a case of fatal systemic anaphylaxis to gadobenate, with massive hemorrhage, associated with elevated beta-tryptase, causing fibrinogenolysis and impairing fibrinogen ability to undergo thrombin-mediated fibrin formation.

TO THE EDITOR:

Anaphylaxis to gadolinium occurs in 0.001% to 0.01% of administrations. Although it has increased over the last decades, gadolinium is considered to be very safe, rarely associated with death.¹

A 64-year-old woman with personal history of hypertension, ex-smoker, dyslipidemia, and obesity was diagnosed with septum hypertrophic cardiomyopathy after a first episode of atrial fibrillation with spontaneous cardioversion. Ventricular ejection fraction was normal and she was in class I-II/IV for dyspnea. She was being treated with atenolol, lisinopril, rosuvastatine, torasemide, and acenocoumarol. She had no history of atopy, drug allergy, or asthma and she had never been exposed to gadolinium-based contrast media.

She presented at the outpatient clinic to undergo a cardiac magnetic resonance. The patient's medications were not discontinued before the study. At her arrival, her blood pressure was 170/80 and heart rate (HR) was 45 bpm. Intravenous gadobenate dimeglumine (20 mL) (Multihance, Bracco Diagnostics Inc., Cranbury, NJ) was administered. Two minutes later, she complained of malaise and myalgia, and 1 minute later showed a decreased level of consciousness. The procedure was immediately stopped. At that time, physical examination showed cyanosis, HR 40 bpm, systolic blood pressure 80 mm Hg, and oxygen saturation 85%. Epinephrine, dexchlorfeniramine, and hydrocortisone were administered. The patient went into cardiorespiratory arrest with asystole. Advanced cardiopulmonary resuscitation was initiated with intravenous epinephrine, fluids, bicarbonate, and norepinephrine, followed by use of an Extra Corporeal Membrane Oxygenation device. A 20-cm hematoma developed on her thighs at the site of vascular punctures along with massive gastrointestinal bleeding (>3 L), through nasogastric and orotracheal tubes. Blood tests showed pH 6.81, PaCO₂ 29 mm Hg, HCO₃ 5 mEq/L, lactate more than 15 mM, a decreasing hemoglobin (8.2 to 5.1 g/dL), and low platelet

($88 \times 10^9/L$) count. Fibrinogen and clotting time tests were undetectable despite treatment with vitamin K, protamine sulfate, coagulation factor concentrates, and fresh frozen plasma together with red cell and platelet transfusions. Unfortunately, hemodynamic control was not achieved and the patient died within 20 hours of the gadolinium injection.

A serum sample obtained from the femoral artery 50 minutes after the onset of symptoms reported 63 ng/mL for total tryptase (normal, <11.4 ng/mL) (UniCAP, Phadia, Thermo Fisher, Upsala, Sweden) and 17 ng/mL for mature beta-tryptase (normal, <1 ng/mL) (Virginia Commonwealth University, Richmond, Va).

Serum tryptase is a biomarker for systemic anaphylaxis. Pro- α/β -tryptases are continuously secreted from mast cells (MCs) as inactive proenzymes. The level of protryptase reflects genetic factors,² and also the total body MC burden, whereas mature tryptases are stored in MC granules and released as tetramers, including active beta-tryptase, upon MC activation.³ Total tryptase levels are elevated at baseline in most patients with systemic mastocytosis, whereas beta or total tryptase levels peak about 1 hour after clinical onset of systemic anaphylaxis, and then decline, returning to baseline by about 4 hours.³ A total tryptase assay, which is widely available, measures both α/β , pro/mature tryptases. High total tryptase levels are found after anaphylaxis, but these must be compared with the respective baseline levels to distinguish between MC activation and increased MC burden.³ In turn, an increased beta-tryptase level (available from LBS Lab in Virginia) is the pathognomonic finding in systemic anaphylaxis with ratios of total to beta-tryptase typically being less than 10.³

Measuring beta-tryptase is essential to diagnose postmortem anaphylaxis, when a baseline blood sample is not available.⁴ An elevated beta-tryptase level in serum (>10 ng/mL) increases the likelihood that anaphylaxis caused the death.³ However, high tryptase values have also been found in deaths of other causes, casting uncertainty as to how MCs were activated to release this protein, but nevertheless, still raising the possibility of an MC activation–related death.^{4,5} Also, MC lysis, conceivably, may increase tryptase levels in blood, so postmortem serum samples should be taken as soon as possible and from peripheral blood vessels.⁵

Laroche et al⁶ compared total tryptase blood levels in patients with severe allergic reactions during anesthesia and patients with shock from other causes, including patients with cardiac arrest, showing that resuscitation maneuvers and treatment of shock, by themselves, did not induce an increase in tryptase levels. An elevated tryptase level strongly supported MC activation and the diagnosis of anaphylaxis.⁶

In this patient, we found high total and beta-tryptase levels in a serum sample extracted from a femoral artery 1 hour after the onset of symptoms, with a total/beta-tryptase ratio of 3.7, indicating premortem MC activation. Whether gadobenate-induced anaphylaxis was IgE-mediated was not addressed, because allergy skin tests could not be performed and an *in vitro* drug-specific IgE test has not yet been developed. Previous treatment with β -blocker and angiotensin-converting enzyme inhibitor drugs could have blunted the physiologic

response to hypotension, thereby influencing the fatal outcome. There was no previous exposure to gadolinium, but hypersensitivity reactions to contrast media occur in 30% of patients at first exposure.¹ No other risk factors for severe anaphylaxis were apparent. Additional studies addressing potential risk factors such as obesity, hypertension, or medication and the role of potential biomarkers such as gadolinium skin tests or basal serum tryptase level are needed to identify patients at risk and to adopt preventive measures.

Autopsy was not performed and there was no evidence for any underlying malignancy. The final cause of death was cardiac arrest in association with a significant bleeding diathesis. Fibrinogen can be cleaved by beta-tryptase, impairing its ability to undergo thrombin-mediated fibrin formation.⁷ Indeed, fibrin deposits were markedly increased in the skin of tryptase-deficient mice subjected to a passive cutaneous anaphylaxis reaction.⁷ Beta-tryptase prolongs the thrombin-dependent clotting time in human plasma samples.⁷ Therefore, the anticoagulant activity of beta-tryptase likely contributes to prolonged activated partial thromboplastin time or prothrombin time values and to hemorrhagic episodes reported in patients with anaphylaxis or mastocytosis.^{8,9} Undetectable fibrinogen levels and prolonged clotting times in our patient were likely related to massive MC activation, releasing beta-tryptase. Heparin, stored in MC secretory granules and released in parallel with tryptase, also inhibits thrombin-mediated clotting. Therefore, it has been proposed as the relevant anticoagulant factor released from activated MCs. However, heparin has shown less *in vitro* anticoagulant activity than beta-tryptase.⁷ Moreover, protamine administered to our patient did not revert hemorrhage and prolonged clotting times. Platelets would be incidentally decreased because of consumption as well as because of the Extra Corporeal Membrane Oxygenation device. In addition, anaphylaxis could lead to disseminated intravascular coagulation, which could also explain the coagulopathy, although D-dimer fragment levels were not measured.¹⁰ In that case, fibrinogen levels decrease although rarely to undetectable levels. Whether MC activation may be present in all cases of disseminated intravascular coagulation or not has not been evaluated.

In conclusion, considering the high total and beta-tryptase levels, we propose that systemic anaphylaxis to gadobenate was the cause of death in this patient, with hemorrhage occurring because of the secretion of β -tryptase, causing fibrinogenolysis. This cause of acute hemorrhage appears to be understudied and underrecognized. Measuring mature tryptase levels in more cases of suspected anaphylaxis associated with bleeding would better indicate the prevalence of this event, and raise the question of whether tryptase inhibitors could impact their outcomes.

^aDepartment of Allergy, University Hospital Gregorio Marañón, Health Research Institute Gregorio Marañón, Madrid, Spain

^bDepartment of Cardiology, University Hospital Gregorio Marañón, Health Research Institute Gregorio Marañón, and Complutense Medical School, Madrid, Spain

^cDepartment of Internal Medicine, Virginia Commonwealth University, Richmond, Va

^dDepartment of Hematology, University Hospital Gregorio Marañón, Health Research Institute Gregorio Marañón, and Complutense Medical School, Madrid, Spain

^eDivision of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

Conflicts of interest: L. B. Schwartz has received consultancy fees from Sanofi Aventis, Dyax, ViroPharma, and HELIX; has received research support from CSL Behring, Dyax (Shire), and Merck; receives royalties from Virginia Commonwealth University Innovation Gateway; and has received payment to participate in the "Atopic Dermatitis in America" study from Asthma and Allergy Foundation of America. M. C. Castells has received consultancy fees from Genentech, Merck, and Sanofi; is employed by Brigham and Women's Hospital; has received research support from Ovarian Cancer Research; has received lecture fees for numerous lectures; and receives royalties from UpToDate. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication March 20, 2017; revised May 1, 2017; accepted for publication May 9, 2017.

Available online June 19, 2017.

Corresponding author: Alicia Prieto-García, MD, PhD, Servicio de Alergia, Hospital General Universitario Gregorio Marañón, Dr Esquerdo, 46, 28007 Madrid, Spain. E-mail: alicia.prieto@salud.madrid.org.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2017.05.008>

REFERENCES

1. Raisch DW, Garg V, Arabyat R, Shen X, Edwards BJ, Miller FH, et al. Anaphylaxis associated with gadolinium-based contrast agents: data from the Food and Drug Administration's Adverse Event Reporting System and review of case reports in the literature. *Expert Opin Drug Saf* 2014;13:15-23.
2. Lyons JJ, Yu X, Hughes JD, Le QT, Jamil A, Bai Y, et al. Elevated basal serum tryptase identifies a multisystem disorder associated with increased TPSAB1 copy number. *Nat Genet* 2016;48:1564-9.
3. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am* 2006;26:451-63.
4. Busardò FP, Marinelli E, Zaami S. Is the diagnosis of anaphylaxis reliable in forensics? The role of β -tryptase and its correct interpretation. *Leg Med (Tokyo)* 2016;23:86-8.
5. McLean-Tooke A, Goulding M, Bundell C, White J, Hollingsworth P. Post-mortem serum tryptase levels in anaphylactic and non-anaphylactic deaths. *J Clin Pathol* 2014;67:134-8.
6. Laroche D, Gomis P, Gallimidi E, Malinovsky JM, Mertes PM. Diagnostic value of histamine and tryptase concentrations in severe anaphylaxis with shock or cardiac arrest during anesthesia. *Anesthesiology* 2014;121:272-9.
7. Prieto-García A, Zheng D, Adachi R, Xing W, Lane WS, Chung K, et al. Mast cell restricted mouse and human tryptase-heparin complexes hinder thrombin-induced coagulation of plasma and the generation of fibrin by proteolytically destroying fibrinogen. *J Biol Chem* 2012;287:7834-44.
8. Moreno-Ancillo A, Gil-Adrados AC, Domínguez-Noche C, Jurado-Palomo J. Bleeding and shock in a 44-year-old woman with systemic mastocytosis. *J Invest Allergol Clin Immunol* 2013;23:504-21.
9. Lombardini C, Helia RE, Boehlen F, Merlani P. "Heparinization" and hyperfibrinogenolysis by wasp sting. *Am J Emerg Med* 2009;27:1176.
10. Wada H, Matsumoto T, Yamashita Y. Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care* 2014;2:15.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.