



Contents lists available at ScienceDirect

Legal Medicine

journal homepage: www.elsevier.com/locate/legalmed

Case Report

Mast cell tryptase in a case of anaphylaxis due to repeat antibiotic exposure

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ARTICLE INFO

Article history:

Received 5 January 2009

Received in revised form 25 April 2009

Accepted 27 April 2009

Available online xxxx

Keywords:

Mast cell tryptase

Anaphylaxis

Cefazolin

Lupus

Dialysis

ABSTRACT

Mast cell tryptase can be an indicator of type I hypersensitivity reaction and thus may serve as a surrogate marker of anaphylaxis. A 34-year-old white male patient presented with a history of systemic lupus erythematosus. Shortly after administration of cefazolin for dialysis, he developed pruritis and shortness of breath. He expired an hour later. Autopsy excluded anatomic causes of death. There was an elevated postmortem mast cell tryptase level, 29.2 ng/mL. For mast cell tryptase level to be useful, the patient must survive long enough after exposure to an allergen for mast cells to release this enzyme. A credible allergen must be identified. In this case such, mast cell tryptase could establish anaphylaxis as the cause of death. The case suggests that in a patient with autoimmune disease, it may be prudent to test for immune reaction to a drug before administering it a second time via pinprick or other method.

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1. Introduction

Postmortem diagnosis of anaphylaxis has traditionally been based on circumstantial evidence, including history, scene investigation, and nonspecific autopsy findings [1,2]. The development of assays for chemical markers of allergic reactions, however, has offered new tools in investigating deaths which appear to be due to anaphylaxis [1,3,4].

Mast cell tryptase is one such marker. This enzyme is a neutral protease of mast cells which can be an indicator of their activation and degranulation in allergic reactions [2–7]. In type I hypersensitivity reaction, previous exposure to an antigen leads to sensitization of the immune system by production of immunoglobulin E (IgE) that is specific for the antigen [8], although there may be significant cross-sensitivity with related antigens [9]. On subsequent re-exposure to the antigen, the previously-generated IgE binds to mast cells and basophils, releasing bioactive substances which cause smooth muscle around blood vessels and bronchi to constrict [1,8]. Symptoms may be local or systemic [8,10], and bronchospasm or cardiovascular collapse may develop in severe cases, which can be fatal [10].

Since mast cell tryptase is a product of the cascade of type I hypersensitivity reactions, it might serve as a surrogate marker of anaphylaxis [2–4]. Such a marker can be useful, both in clinical practice and in forensic pathology, since an autopsy of allergic reaction may produce no pathognomonic findings [11], but anaphylaxis is the presumptive cause of death in some 1500 cases in

the United States each year [12]. Such a case was recently identified, in which anaphylaxis was a candidate in the differential diagnosis of death, and was presumptively clinically observed. However, there was a complicated medical setting that did not have an obvious cause of death, including anaphylaxis. An autopsy excluded other common causes of death, even most of them specific for this patient, but did not yield a final anatomic answer. The history of medication use, clinical effect following administration of medication, and measurement of mast cell tryptase instrumental in establishing the cause of death. The case also provides possible guidance for managing drug administration in a patient with known atopic phenotype or otherwise active immune disorder, such as the autoimmune condition of lupus.

2. Case report

The decedent was a 34-year-old white male with a history of systemic lupus erythematosus who was on dialysis for end-stage renal disease. He was obese and had chronic stasis ulcers on one leg, with episodes of cellulitis. He had a surgical history of aortic valve replacement due to an aortic valve deformity which led to embolic disease to the eyes. On admission for dialysis, the patient presented with his standing medical problems, and he had experienced a recent upper respiratory tract infection. His admission lab tests showed severe anemia, hemoglobin concentration 4.6 g/dL, hematocrit 17.4%, consistent with the end-stage renal disease and lack of erythropoietin production. Due to his chronic cellulitis and the upper respiratory tract infection, he was given was given intravenous cefazolin for prophylaxis. This was a drug which he had been given only once before during dialysis to manage

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cellulitis prophylactically, and he had tolerated it well, with good clinical outcome. On this admission however, within 10 min of administration of the cefazolin, the patient complained of pruritis and demonstrated shortness of breath. The evidence of these symptoms so soon after administration of medication rightly prompted concern over a possible allergic reaction, so the antibiotic was discontinued and he was given intravenous diphenhydramine. However, the patient suffered a seizure and respiratory arrest within 20 min. He was intubated, but could not be adequately ventilated. He expired an hour later.

Based on his history, the patient was considered to have been at risk for several potentially fatal conditions, including heart disease related to obesity, cardiovascular disease, prosthetic aortic valve, or lupus; renal failure; infectious disease, such as recent upper airway infection or sepsis from chronic stasis ulcers; cerebrovascular accident related to obesity, previous embolic disease, prosthetic valve, lupus, or steroid treatment; pulmonary embolus due to obesity and stasis; and anaphylaxis. Since none of these causes was obvious, an autopsy was ordered.

External examination showed an obese young white man. An endotracheal tube was in place in the upper airway. An arteriovenous fistula was identified on the right arm, and cellulitis was observed on the left distal leg. The internal examination showed a large heart, status post aortic valve replacement by a St. Jude prosthetic valve. The lungs were edematous. The liver had yellow-brown parenchyma. The small kidneys were granular. The brain was edematous, negative for hemorrhage.

On microscopic examination, the coronary arteries showed mild atherosclerosis. The lungs showed diffuse hemorrhages with anthracosis. The kidneys showed very extensive glomerulosclerosis with fibrosis and chronic inflammation consistent with end-stage lupus nephritis. The liver showed 2+ fatty change consistent with obesity and therapeutic steroid use.

Toxicology was negative for alcohol and drugs of abuse. Serum mast cell tryptase level, determined by a fluoroenzyme immunoassay, was 29.2 ng/mL (normal <11.5 ng/mL). Serum cefazolin concentration was low, 48 ng/mL (therapeutic peak range 60–120 ng/mL), consistent with discontinuation of the intravenous administration of the antibiotic.

Postmortem lung and blood cultures were negative for growth.

3. Discussion

The autopsy excluded cardiovascular, cardiac valvular, embolic, cerebrovascular, toxicologic, infectious, and hemorrhagic causes of death. Pulmonary edema was nonspecific, but was consistent with allergic reaction. The autopsy excluded candidate anatomic causes of death for this man, and elevated postmortem mast cell tryptase level indicated anaphylaxis. The patient was diagnosed as suffering from a fatal acute anaphylactic reaction, probably from a reaction to cefazolin, to which he had been documented to have had one previous exposure during an earlier dialysis treatment. This first exposure possibly sensitized his immune system to antigens of this antibiotic, leading to anaphylaxis on second exposure, and death.

Mast cell tryptase can be considered a surrogate marker for anaphylaxis, but not categorical evidence of immune reaction by itself. Its value is taken in the context of this patient with the clear-cut history of single previous use of cefazolin as a treatment, suggesting opportunity for exposure and sensitization, followed by secondary development of immune-mediated reaction on a following exposure. There were clear clinical indications of anaphylactic reaction following use of the drug on the second exposure. And, there was diminished, but incomplete, recovery from the reaction after discontinuation of the medication and treatment for anaphylaxis, also possibly explaining the relatively lower postmortem mast cell tryptase levels.

Like most cases of anaphylaxis, anatomic autopsy findings in this case were nonspecific [11]. Such findings may include features such as laryngeal edema and hyperinflated lungs with bronchial mucous plugging [6,8,11]. In one previously-reported case, degranulating mast cells were identified in the larynx [8]. The etiologies of the anaphylactic reactions which have been reported are varied, too. Mast cell tryptase has been used to assist in determining anaphylaxis caused by various antigens, both antemortem and postmortem. Interestingly, medical agents are relatively rare contributors to anaphylactic deaths. Documented cases include anesthetic agents [9], muscle relaxants, latex [10], and fluorescein [5]. The present case is unusual in that a fairly common source of allergic reactions in other settings, antibiotics, caused a relatively rare fatal anaphylaxis, although other cases have been documented using both mast cell tryptase and chymase [13].

By contrast, mast cell tryptase levels have been documented for deaths from numerous biological allergens such as amniotic fluid embolism [3,7], dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) [1], honey bees (*Apis mellifera*), [6,14] fire ants (*Solenopsis invicta* and *Solenopsis richteri*), [15] and an unusual case of pancake mix infected with molds *Penicillium*, *Fusarium*, *Mucor*, and *Aspergillus* [8]. A comparative summary of these cases and mast cell tryptase concentrations is provided in Table 1.

Because the range of mast cell tryptase illustrated by the preceding cases is so large, even in some non-allergic deaths, and the effect of different antigens appears to induce different degrees of mast cell degranulation, it is not clear that an elevated mast cell tryptase level by itself is sufficient for forensic purposes to establish anaphylaxis as the cause of death. The present case fortifies the value of the use of mast cell tryptase as a surrogate test for anaphylactic cause of death, however, thanks to the documented clinical symptoms that emerged after the documented second administration of a drug that had only been used once previously in the dialysis setting.

While postmortem elevations of mast cell tryptase levels are useful to support the diagnosis of anaphylaxis as the cause of death, this test must be interpreted with caution. A fundamental limitation of the test's utility is that the decedent must have survived long enough for mast cells to have degranulated and for mast cell tryptase to have entered the systemic circulation. In documented cases of anaphylaxis, the amount of time from introduction of the allergen to death ranges from 37 min to one hour [6,7]. The present case demonstrates this principle as well, since the patient survived one hour before succumbing to anaphylaxis. In massive acute anaphylaxis, however, the patient may expire from shock before mast cell tryptase levels can become elevated. It is possible that the relatively low elevation of mast cell tryptase in this patient is due to death from anaphylaxis before the mast cells could degranulate to produce much higher levels seen in other cases.

Table 1
Reported values of mast cell tryptase in different studies.

Reference	Author	Year	Antigen	ng/mL
Present	Carson	2009	Cefazolin	29.2
[8]	Bennet	2001	Mold	14.0
[1]	Edston	2003	Dust mite	170, 200
[15]	Prawlow	1998	Fire ant	12.0
[3]	Nishio	2002	Amniotic fluid	67.2
[7]	Farrar	2001	Amniotic fluid	4.7
[2]	Horn	2004	Normal	<11.4
[4]	Schwartz	2004	Normal	1.0–15.0
[16]	Randall	1995	Non-anaphylactic	1–5 (24 cases) 5–10 (2 cases) >10 (5 cases)

There are factors in mast cell tryptase determination which may confound the use of this assay. One such factor is the native level of this enzyme. A study of 49 autopsy cases in which there was no expectation of anaphylaxis showed that five cases had a level of greater than 10 ng/mL, one even reaching 106 ng/mL [16]. Mast cell tryptase can also be elevated in reactions due to direct histamine release [4,9], and one study suggests that a prolonged post-mortem interval can increase the level of mast cell tryptase [2], although this finding has also been discounted in another study [16]. Another confounding factor is competing disease, such as sudden infant death syndrome [17] and heart disease or chest trauma [2,18].

A further consideration in using mast cell tryptase for forensic purposes is the analyte stability over time, especially if the specimen is not drawn or analyzed promptly, for example if the body is not found immediately. We did not have this concern, since the decedent died in hospital and was autopsied within two hours of death. However, study of this enzyme has been shown to be stable for 2–4 days after acquisition [19]. Frozen specimens are preferred for analyte stability for a longer period, but even a room temperature specimen can be acceptable for up to 4 days [19].

The initiator of mast cell degranulation, IgE, has been proposed as an adjunct for assessing the relevance of mast cell tryptase elevations in postmortem specimens [2]. This analyte also may be increased with prolonged postmortem interval, however, so its value in establishing mast cell degranulation is questionable [2]. Perhaps more useful is determination of allergen-specific IgE [2,11,14,15], because the titer of IgE to the offending antigen could indicate immune activation. Prospectively, the activity of allergen-specific IgE can be useful to avoid allergic and anaphylactic reactions by skin-prick, intradermal testing, or serologic assay [9,10].

Such options were not available to the present patient, of course, as he had been apparently sensitized by an earlier dose of cefazolin, and the development of an allergy to this drug was not known until the second dose led to anaphylaxis. The case suggests that the risk of anaphylaxis in a patient with an atopic trait or known autoimmune disease, however, may warrant extra care when administering a drug for a second time, such as a skin-prick or other test with a limited exposure to the drug, to determine if the first experience with the drug may have led to sensitization and could induce anaphylaxis on subsequent use.

The present case demonstrates the utility of mast cell tryptase as an adjunct to implicating or establishing anaphylaxis as a cause of death. The anatomic procedures of the autopsy allowed exclusion of other potential causes of death, and the mast cell tryptase determination showed an elevation which supported the documented clinical observation of allergic reaction. The association of elevated mast cell tryptase in a case of anaphylactic reaction

to an antibiotic in a forensic case is useful. In addition, this case demonstrates the relevance of mast cell tryptase determinations even in a patient with advanced autoimmune disease. Thus, with prudent use of history and autopsy findings, mast cell tryptase may be a valuable tool in diagnosing anaphylaxis, and can be an adequate test for use in forensic cases.

Conflict of interest

No conflict of interest is created by the reviewing this case and its findings.

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