Case Report

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Death Due to Furosemide Anaphylaxis and The Importance of Serum Tryptase Level in Diagnosing Anaphylaxis: A Case Report

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Abstract

Anaphylaxis is a severe systemic hypersensitivity reaction with a sudden onset and may result in death. In this study, we report the case of a 71-year-old female patient who died within seconds after the administration of intravenous furosemide in emergency service; shehad high serum tryptase levels at postmortem examination and nonspecific findings at autopsy, and death due to anaphylaxis was reported. With this study, we wanted to point to the rare and potentially fatal drug anaphylaxis, such as furosemide anaphylaxis. Also, our results indicate the importance of serum tryptase levels in the diagnosis of death due to anaphylaxis.

Keywords: Furosemide, anaphylaxis, postmortem diagnosis, serum tryptase levels

Introduction

Anaphylaxis is an immunoglobulin E (IgE)-mediated hypersensitivity reaction that can cause cardiovascular collapse within minutes (1). Triggers for anaphylaxis include drugs, foods, insect stings, and animal bites (2). Furosemide-induced anaphylaxis has not been extensively reported in the studies performed thus far. Our literature review yielded 4 case reports of furosemide anaphylaxis. Death was reported in 2 of the 4 case reports (3–5).

In this study, we report the case of a 71-year-old female patient who died within seconds after the administration of intravenous furosemide, and her cause of death was determined by autopsy as anaphylaxis. We have discussed the importance of serum tryptase levels in the diagnosis of death due to furosemide anaphylaxis and anaphylaxis in light of the findings reported in the literature thus far.

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Case Report

We report the case of a 71-year-old woman who was receiving medical treatment for approximately 8 years for chronic obstructive pulmonary disease and essential hypertension. She was taking furosemide tablets and ampoules intermittently in the previous year. In medical records, furosemide was prescribed five months before her death, a box of 12 tablets, and about seven months ago, a box of 5 ampoules. She used furosemide at the time it was prescribed. In the medical history of the case, she was treated in the hospital with the complaint of rash after the use of analgesic drugs. However, there is no history of allergy-related to previous use of furosemide. On the day of the incident, she was admitted to the emergency department with a complaint of shortness of breath. Physical examination of the patient showed body temperature, 36.5 °C; arterial blood pressure, 190/110 mmHg; pulse, 113/min, respiratory rate; 22/min, oxygen saturation (SpO_2), 98 (in room air); decreased inspiration; increased expiration; and hyperemia in the tonsils. The results of biochemical tests like urea (44.00 mg/dl - on the day of incident) and creatinine (1.25 mg/dl - on the day of incident) and complete blood count were within normal limits. Antihypertensive treatment included 2 ampoules of furosemide (Lasix®) administered as an intravenous push, but the condition of the patient started deteriorating drug administration, and cardiopulmonary arrest developed within seconds. Considering that an allergic reaction had developed, an antiallergic treatment was administered for anaphylaxis. However, the case did not respond to the medical intervention, and she died. Because of the sudden death, the case was considered to be a forensic case, and a declaration was submitted to the prosecutor's office.

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An autopsy was performed within 24 hours of the death of the case. External examination observed needle puncture marks on the dorsal side of both hands and the left elbow because of medical intervention as a positive finding. At autopsy, venous engorgement was observed on the brain surface and petechial hemorrhage was observed in the brain sections. The uvula had a mild edematous appearance. No macroscopic edema was observed in the epiglottis, vocal cords, larynx, and trachea. Anthracosis and petechiae were present on both lung surfaces. Right lung weight was 590 gr., left lung weight was 550 gr. Slight edema and congestion were seen in the lung sections. Heart weight was 580 gr. Moderate atherosclerotic narrowing of the coronary arteries was observed. No abnormal findings were observed in the abdominal organs.

Results of histopathological examination showed intra-alveolar fresh bleeding, edema, and ruptured capillaries in the lungs; subepithelial chronic nonspecific inflammation, edema, and extravasated erythrocytes in the uvula, epiglottis, and larynx (Figure 1, 2); areas of fibrosis secondary to cardiac ischemia and signs of hypertrophy; and a moderate atherosclerotic narrowing and locally calcified plaque was observed in the left coronary artery.

Toxicological analyses of the samples obtained from the heart and femoral blood were performed using quadrupole time-of-flight (X500R; Sciex®, Toronto, Canada) and gas chromatography-mass spectrometry (GC-MS; QP 2010; Shimadzu®, Kyoto, Japan) in toxicology laboratory of our Forensic Medicine Institute. Paracetamol (402 ng/mL) and Pheniramine (47.7 ng/mL) were detected in the samples. Furosemide was not detected in the blood using both methods of analysis. Diltiazem, Chlorpheniramine, andTrazodone were detected in the urine.

Measurement of serum tryptase levels could not be performed at our institution; therefore, the sample was sent to an accredited private laboratory in a box covered with dry ice for analysis. The results of the analysis showed a serum tryptase level of 199.00 ng/mL.

No criminal element was found in the crime scene investigation by the prosecutor's office. Based on witness statements, medical documents, the manner of death, autopsy findings, and findings of high serum tryptase level, a report was prepared to indicate that the death of the case as a result of anaphylaxis due to furosemide.

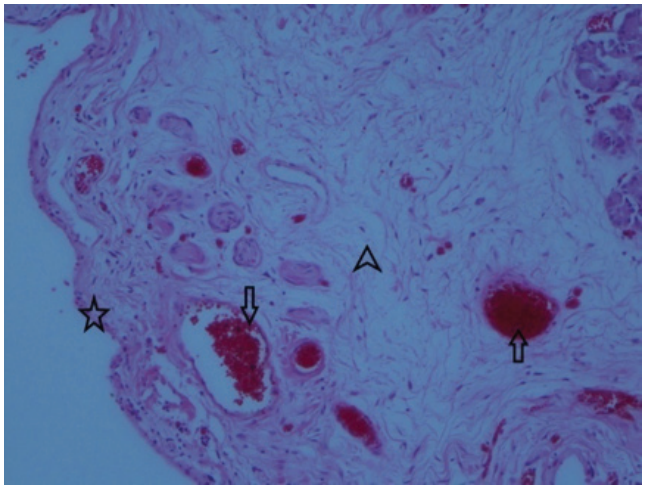

Figure 1: Larynx, shedding of the surfaceepithelium, dilated congested vascular structures in the subepithelial space, and edematous stroma (Arrow: congested vascular structures, Arrowhead: edema in the stroma, Star: surfaceepithelial area (shed) (H&E; x10)

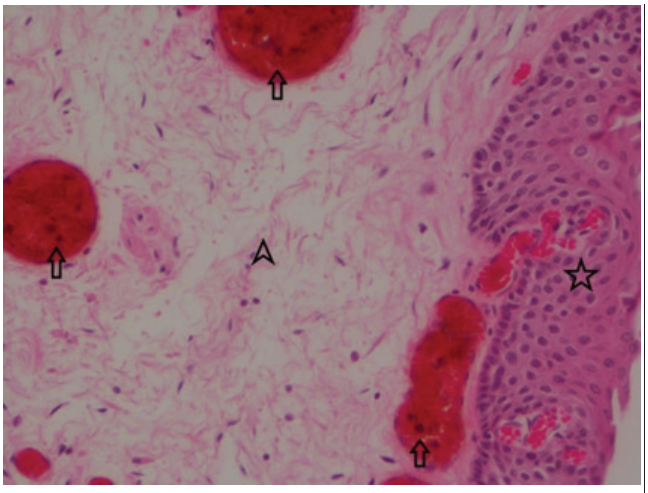

Figure 2: Uvula, congestion of the surfaceepithelium dilated congested vascular structures, and edematous stroma in the subepithelial space (Arrow: congested vascular structures, Arrowhead: edema in the stroma, Star: surfaceepithelial area)(H&Ex20)

Discussion

In this study, we presented a case of death due to furosemide anaphylaxis. According to our literature review, this is the first case report of furosemide-induced anaphylaxis in Turkey. Anaphylaxis was diagnosed by postmortem examinations like postmortem serum tryptase level. Diagnosing anaphylaxis in emergency rooms can be difficult, as some patients' conditions may be misdiagnosed as myocardial infarction and asthma-related death (6). At the same time, postmortem diagnosis of anaphylaxis is difficult for forensic experts because of nonspecific findings.

Classically, in cases of allergy/anaphylaxis, symptoms such as urticaria, itching, rash, edema, and respiratory distress develop acutely and can be seen by the clinician. In postmortem diagnosis, unfortunately, classical findings are not usually seen in these cases. For postmortem diagnosis of anaphylaxis, witness statements must be recorded, a comprehensive crime scene examination must be carried out, a detailed medical history examination for allergens, a detailed external examination, and an autopsy must be performed. In addition, additional tests to determine postmortem serum tryptase level, total IgE level, and allergen-specific IgE level should be performed (6).

Serum tryptase values are between 1–15 ng/mL in a healthy person, and the mean value is 5 ng/mL (7). In the 2010 Working Conference on Mast Cell Disorders, 80% of the members agreed that the acute serum total tryptase level should be at least 20% plus 2 ng/ml over the baseline level (peak mast cell tryptase ≥ (1.2 x baseline tryptase +2 ng/mL)) to be indicative of mast cell activation such as anaphylaxis (8, 9). Tryptase remains stable in the blood, and therefore, significant results can be obtained even if the autopsy is performed

days after death in the postmortem period (6). In corpses with postmortem serum tryptase levels<100 ng/mL, it can be concluded that death may have been due to anaphylaxis if the clinical and autopsy findings are consistent (6). The threshold level of tryptase in corpses with anaphylaxis is 53.8 ng/mL (10). Additionally, we found that the serum tryptase level in our case (199 ng/mL) was well above the threshold value reported previously. Thus, the high levels of serum tryptase in our case were significant for the diagnosis of anaphylaxis.

Old age and chronic diseases like previous cardio vascular morbidity, and chronic obstructive pulmonary disease are risk factors for fatal drug anaphylaxis (11). Previous studies indicate that although serum tryptase levels are higher than normal in corpses who die because of acute cardiovascular diseases, these levels are not above the thres hold value (12,13). Our case had a history of chronic obstructive pulmonary disease and essential hypertension. Histopathological examination at autopsy showed areas of ischemia in the heart and moderate atherosclerotic narrowing in the coronary arteries. In our case, we found the serum tryptase level to be much higher than the levels found in deaths due to cardiovascular diseases. This postmortem-detected high level of tryptase indicated that the subject did not die of cardiovascular disease (3-5).

Determining the causative agent of anaphylaxis is important for diagnosis. However, in many patients with anaphylaxis, identification of the allergen is not possible. Although skin and mucous membrane symptoms are the most common signs in the diagnosis of anaphylaxis, they may sometimes be absent. Laboratory tests such as serum/plasma tryptase, plasma histamine, and measurement of histamine and histamine metabolites (N-methyl histamine) in 24-hour urine become more important in the diagnosis of sudden shock without urticaria and angioedema-like findings (14). In our case, an allergic reaction developed immediately after the administration of furosemide. However, the factor responsible forcausing anaphylaxis could not be detected by advanced methods of toxicological analysis. This may be due to the inability of furosemide to adequately pass into the circulation due to circulatory arrest as a result of anaphylaxis.

Despite the presence of history and clinical findings suggestive of anaphylaxis, we were unable to detect the allergen responsible for causing anaphylaxis in our case. Findings of anaphylaxis may not be evident at autopsy. In such cases, besides the medical history, witness statements, crime scene information supporting anaphylaxis, and high serum tryptase levels postmortem can be very valuable in the diagnosis of anaphylaxis. Since tryptase remains stable in the blood, if the blood sample is taken and stored under appropriate conditions, significant diagnostic results can be obtained as tryptase analysis can be performed months after the autopsy. Since the serum tryptase level increases in many diseases such as coronary artery disease and mast cell disorders besides anaphylaxis, it is important to know the basal serum tryptase level in the diagnosis of anaphylaxis. Basal serum tryptase value can be obtained by analyzing the samples taken for "complete blood count and routine biochemical tests" in people who applied to the hospital before their death. Then "Peak mast cell tryptase ≥ (1.2 x baseline tryptase +2 ng/mL)" formula can be used for a more precise evaluation.

Conclusion

In conclusion, we present a rare case of death due to intravenous furosemide-induced anaphylaxis that we detected high serum tryptase levels postmortem. In deaths with suspected anaphylaxis, the allergen may not be known or detected. Signs of anaphylaxis may not be evident at autopsy. These factors complicate the postmortem diagnosis of anaphylaxis. In such cases, high serum tryptase levels postmortem can be very important in diagnosing anaphylaxis. In addition, with this study, we wanted to draw attentionto the fact that furosemide, which is frequently used in emergency departments, can cause anaphylaxis, although it is rare.

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