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Short report

Postmortem diagnosis of anaphylaxis in presence of decompositional changes

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ABSTRACT

Eosinophil and activated mast cell identification in the spleen combined with mast cell tryptase determination in postmortem serum may diagnose fatal anaphylaxis with a high degree of certainty. Mast cell tryptase measurement and significance in corpses with decompositional changes remains however an issue of controversy. Analogously, immunohistochemistry in corpses with decompositional changes may be influenced by several mechanisms, including protein alteration, antigen diffusion and unspecific antibody binding to disrupted protein structures. The authors present an autopsy case involving a 55-year-old woman who unintentionally received clarithromycin. Due to difficult in administrative procedures, the postmortem examination was performed 96 h after death. Mast cell tryptase was measured in postmortem serum from femoral, aortic and right heart blood. The obtained results were consistent with mast cell activation. Histochemistry (Pagoda Red) and immunohistochemistry (anti-tryptase antibodies) allowed splenic eosinophils and mast cells to be detected. Based on the results of all postmortem investigations, the hypothesis of anaphylaxis following accidental clarithromycin administration was formulated.

1. Introduction

The accumulation of activated mast cells and eosinophils during anaphylaxis-related deaths in the splenic red pulp has been described by several authors. Most researchers identified eosinophils and activated mast cells in the spleen using specific immunohistochemical staining with monoclonal antibodies. Based on these findings, immunohistochemistry has been suggested as the most reliable diagnostic tool for splenic activated mast cells and eosinophils identification.[1–3]

Nevertheless, the diagnostic potential of specific immunohistochemical staining might be limited or compromised by the autolytic decomposition of morphological structures that occur after death. This raises the questions of whether mast cell tryptase determination in postmortem serum and immunohistochemistry on spleen sections might be supported by other techniques that would allow for a suitable diagnosis of anaphylaxis-related deaths in corpses with decompositional changes.

Here we present an autopsy case involving a 55-year-old woman who unintentionally received clarithromycin. Due to difficult in administrative procedures, the medico-legal autopsy was performed 96 h after death. Based on the results of all postmortem investigations, the hypothesis of anaphylaxis following accidental clarithromycin administration was formulated.

2. Case report

The corpse of a 55-year-old Caucasian woman was found dead in the bedroom of her mother's apartment at 10:00 p.m. The days prior to her death, she complained of upper respiratory tract discomfort, fever and productive cough. The day of her death, she spent the afternoon in her mother's apartment. At 6:00 p.m., the mother called her general practitioner explaining these symptoms on the phone. She did not mention that these afflicted her daughter at any time, implying that she herself personally had the symptoms.

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Since she had suffered from bacterial bronchitis some months previously, the physician prescribed the same antibiotic (clarithromycin) and suggested she start treatment immediately if she still had the drug at home. At 8:00 p.m., the mother gave her daughter a 500 mg clarithromycin pill and left her in the bedroom. She was found dead two hours later. Due to unclear circumstances of death, a medico-legal autopsy was ordered by the public prosecutor.

External macroscopic examination of the corpse was performed by the emergency medical service at the death scene and was unremarkable. The mother reported that her daughter was not suffering from any particular disease. Medical information pertaining to former antibiotic prescription or drug allergies was unavailable.

The location of the death scene (a small, countryside village), timing of events (Friday evening), need for corpse transport (100 km away to the nearest medico-legal center) and administrative procedures of officially designating a forensic pathologist to the case, allowed the corpse to remain at room temperature in a local hospital (in July) for 36 h and in a refrigerated room at the medico-legal center for 60 h before autopsy.

The deceased was 168 cm tall and weighed 80 kg. External examination revealed decompositional changes characterized by diffuse green skin discoloration as well as marbling of upper and lower extremities. Though organs exhibited decompositional changes, mild laryngeal edema could still be noticed. The heart weighed 400 g and did not reveal any hypertrophy or dilatation. The myocardium did not exhibit fibrosis or ischemic areas. The coronary arteries had a normal anatomic course and revealed mild atheromatous disease without significant stenosis. The aorta exhibited mild atheromatous disease. The lungs were relatively edematous and congested (left 600 g, right 650 g), the spleen congested and enlarged (200 g), the brain edematous (1450 g). No other abnormalities were detected.

Small amounts of femoral, aortic and right heart blood were recovered for toxicological and biochemical investigations. Mast cell tryptase was measured in postmortem serum from femoral (46 μg/l), aortic (49 μg/l) and right heart (42 μg/l) blood. Specific IgE anti-clarithromycin could not be measured due to postmortem serum unavailability. Tissue samples from the heart, lungs, kidneys, liver, brain and spleen were processed routinely and stained with haematoxylin-eosin (HE). Spleen samples were also stained with Pagoda Red for eosinophil and mast cell identification. Parallel spleen sections were treated with anti-tryptase antibodies for mast cell identification. The cells were counted in 10 random × 40 fields.

Conventional histology revealed decompositional changes in most organs. Splenic eosinophils and mast cells as well as degranulated mast cells were detected (Pagoda Red), mainly located in spleen sinuses. Immunohistochemistry (anti-tryptase antibodies) confirmed the presence of mast cells in the spleen. Fig. 1.

Systematic toxicological analysis included blood ethanol level determination as well as general screening for volatile and nonvolatile drugs, poisons and metabolites. Toxicology was unremarkable.

Postmortem investigations failed to provide any evidence for other possible causes of death. Hence, the hypothesis of anaphylaxis following accidental clarithromycin administration was formulated. The case was not pursued any further by the public prosecutor.

3. Discussion

Adverse drug reactions are relatively frequent in clinical practice and can be responsible for serious health problems. They are broadly categorized into predictable and unpredictable. Predictable reactions are usually dose dependent, are related to the known pharmacologic actions of the drug and occur in otherwise healthy individuals. Unpredictable reactions, including allergic reactions, are generally dose independent, are unrelated to the pharmacologic actions of the drug and occur in susceptible subjects only.[2]

Clarithromycin is a macrolide characterized by the presence of a 14-carbon-atom lactone ring. It is often used to treat bacterial infections including Helicobacter pylori and commonly serves as a substitute for patients with a penicillin allergy. Allergic reactions associated with the use of macrolides are uncommon and occur in 0.4–3% of treatments.[4–6]

Anaphylaxis is an acute, potentially life-threatening multisystem syndrome caused by the sudden release of mast cell and basophil-derived mediators into systemic circulation. It most often results from immunologic reactions to food, medications, and insect stings, but any agent capable of promoting a sudden, systemic mast cell or basophil degranulation can produce it.[7]

The identification of fatal anaphylaxis is extremely challenging in forensic pathology routine. Diagnosis may not be considered unless it was previously suspected based on anamnesis, circumstantial data or available medical history. Macroscopic and microscopic findings may be non-specific or absent, hence the diagnosis typically relies on circumstantial evidence when available, postmortem investigation results and exclusion of other possible causes of death.[1,2]

Markedly increased concentrations of mast cell tryptase in postmortem serum from femoral or aortic blood have been reported by several authors who examined cases of sudden death in individuals who may have died in the course of hypersensitivity reactions. According to some observations, mast cell tryptase levels can be assessed in postmortem serum even days after death. Nevertheless, other researchers evaluated mast cell tryptase concentrations in postmortem serum carefully and claim that results in specimens collected during autopsy may not be relied upon to the same degree as they are in the clinical setting due to decompositional changes.[1,2,8]

Eosinophil and mast cell identification in the spleen using histology, histochemistry and immunohistochemistry combined with mast cell tryptase determination in postmortem serum from femoral or aortic blood may diagnose fatal anaphylaxis with a high degree of certainty.[1–3,8–11]

However, the usefulness of conventional histology and immunohistochemistry can be significantly limited by tissue autolysis.[12] This leads to the conclusion that the diagnosis of fatal anaphylaxis is even more arduous in corpses with putrefactive decomposition.

Indeed, the use of histological techniques in forensic casework is limited by the autolytic decomposition of morphological structures. Immunohistochemistry is considered especially sensitive to tissue decay due to antigen decomposition. Immunohistochemical methods may be influenced by several mechanisms occurring during postmortem alteration, including protein decomposition, antigen diffusion and unspecific antibody binding in the presence of disrupted protein structures. These limits notwithstanding, some antigens may still be identified in corpses with different degrees of decomposition.[12–14] In a study performed by Thomsen and Held,[15] the diagnosis of myocardial infarction using C5b-$9_{(m)}$ was possible after a longer postmortem interval than with conventional hematoxylin-eosin.

Edston[9] observed that histochemistry (Pagoda Red stain) does not discriminate between eosinophils and mast cells and is not as sensitive as immunohistochemical staining with monoclonal antibodies. He therefore recommended splenic tissue be systematically sampled for immunohistochemistry in cases of suspected anaphylaxis related-death.