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Diagnosis of anaphylactic death in forensics: Review and future perspectives

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ABSTRACT

The diagnosis of anaphylaxis in a pre- or post-mortal phase involves the formulation of problems not yet solved by the international scientific literature, due to the complexity of pathogenic factors and pathophysiological processes that characterizes it. For forensic autopsies, further problems of differential diagnosis arise and often leave the forensic pathologist unable to express an opinion of certainty, as a result of lack of case history, circumstantial and autoptical-histopathological data. Nevertheless, in routine cases the postmortem diagnosis of anaphylactic death continues to be based on exclusion and circumstantial evidence.

The author, after an extensive review of the literature relating to deaths from anaphylaxis of forensic pathological interest, and a discussion of the microscopical and biochemical findings, proposes a diagnostic protocol for forensic purposes and evaluates the diagnostic perspectives enabled by the newly available analytic techniques and markers.

Maybe, the application of omics methodologies could help in the future for anaphylaxis diagnosis.

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1. Introduction

Anaphylaxis is a type I hypersensitivity reaction which clinical symptoms can be mild to severe. It can cause death within few minutes due to cardiovascular collapse (anaphylactic shock), with symptoms like paleness, loss of consciousness, shallow breathing and frequent insensitivity to external stimuli, imperceptible pulse and severe hypotension, as well as angioedema, airway obstruction due to laryngeal oedema. In other occasions, it is presented with more subdued symptoms like nausea, vomiting, giant hives, asthma and wheezing.

It follows contacts with the allergen through the respiratory tract (inhalation) and digestive tract (ingestion), through skin contact or blood. To the latter belongs the iatrogenic anaphylaxis, already reported by several authors in literature [1–9]. Anaphylactic deaths related to hepatic hydatid cyst have recently been published [10–12]. Very uncommon cases concern anaphylactic death secondary to an accidental sting by crown-of-thorn starfish [13], and a bee sting during paragliding activity [14]. Known allergies can be used for suicidal purposes [15].

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The diagnosis of anaphylaxis in a pre- or post-mortal phase involves the formulation of problems not yet solved by the international scientific literature, due to the complexity of pathogenic factors and pathophysiological processes that characterizes it. For forensic autopsies, further problems of differential diagnosis arise and often leave the forensic pathologist unable to express an opinion of certainty, as a result of lack of case history, circumstantial and autoptical-histopathological data [16]. Nevertheless, in routine cases the postmortem diagnosis of anaphylactic death continues to be based on exclusion and circumstantial evidence, and the knowledge of the patient's history and circumstances of death remains of major importance for the forensic pathologist when investigating suspected anaphylactic deaths [17].

Experimental research lines so far covered with histological and chromatographic-electrophoretic analytical techniques, coupled with multiple detection systems, on tissues and body fluids, have underlined the importance of the functional and pathophysiological role of mast cells, eosinophils, IgE, tryptase, in particular β-tryptase, chymase, eosinophilic cationic protein, histamine, etc... Their specific, individual or synergistic, role has not been, however, useful for formulating a diagnosis of certainty and/or high likelihood of anaphylaxis, which is relevant in the causation of the pre-mortal syndrome and the death [3,18–20].

2. Microscopical findings

The symptoms of anaphylaxis are mainly due to the combined action of vasodilatation, increased permeability of capillaries and smooth muscle contraction caused by the activation of effector cells: mast cells and blood basophils, which are activated through IgE-mediated or IgE-independent pathways (C5a complement, IL-3 cytokines and nerve growth factor) [21].

Consequently, histopathological examination will concern laryngeal oedema, bronchial constriction and acute pulmonary emphysema (Fig. 1a), tracheobronchial secretions, which combined with the exfoliation of the bronchial epithelium, determine the formation of mucus plugs (Fig. 1c), congestion and intra-alveolar haemorrhages, congestion and oedema of major organs, etc...

Nevertheless, these findings are not exhaustive and specific for the diagnosis of fatal anaphylaxis, and a differential diagnosis with asthma can be necessary (Fig. 1b and 1d).

So far, studies have mainly focussed on mast cells, the most important effector cells of anaphylaxis. The evaluation of basophils – other key cells implicated in anaphylaxis-bounces technical problems, and their low blood levels resulted in their role being consistently underestimated [22].

As known, mast cells are found in connective tissue, especially skin and perivascular, and in the bronchial, respiratory and intestinal mucosa. Commonly, immunohistochemistry (IHC) is used for detecting the presence of mast cells in tissues by anti-tryptase and anti-chymase antibodies. Sandwich IHC techniques allow to identify both simultaneously. While IHC with anti-tryptase antibodies is largely used, chymase has been poorly studied in the post-mortem tissues probably because of technical problems related to the paraffin-embedded tissue processing [8,23,24].

Nevertheless, it is important to bear in mind that the diagnosis of an anaphylaxis case only based on the anti-tryptase+ mast cells number is not reliable. Mast cells live in many tissues and play a role in tissue remodelling, angiogenesis, fibrosis and tumor growth, aside from anaphylaxis and allergic inflammation. Recently, the number of mast cells has been proved increased in lungs perivasal areas following asphyxia [25]. Their number is individual-dependent. For this reason, only the tryptase degranulation detection, through IHC with anti-tryptase antibody, if very abundant, can be related to anaphylactic processes (Fig. 2) [26].

It could be useful to compare the number of mast cells and their degranulation rate by performing IHC with specific markers for mast cells, in addition to anti-tryptase antibody. anti-stem cell factor (SCF) antibody is specific for the activated form of the most important mast cell growth factor and differentiation marker (stem cell factor, or KIT-ligand). Using IHC with anti-SCF antibody allows

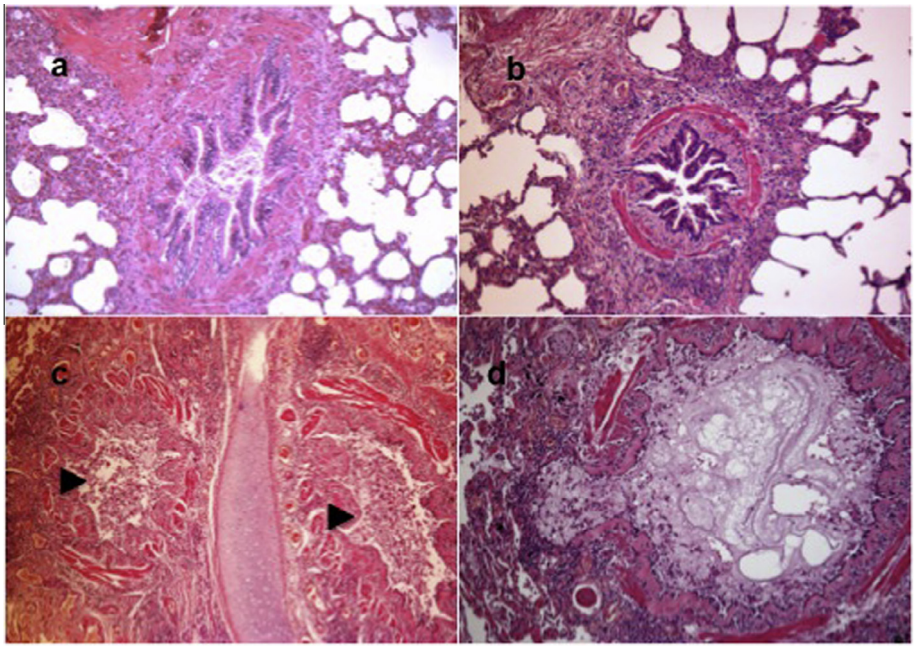

Fig. 1. Bronchial constriction and acute emphysema in a case of anaphylaxis (1a) and in asthma (1b). Note the hypertrophy of the smooth muscle layer and the intense contraction of the ciliated cuboidal epithelium in asthma (1b) compared to a looser one in anaphylaxis. Tracheobronchial secretions and exfoliation of the bronchial epithelium (arrowheads) results in a plug of mucus in a case of anaphylaxis (1c). The inspissated mucus, in which no cells are found inside the plug, is typical of the chronicity of asthma (1d) (H.E., 10x).