

and also other related variables to mortality to get the adjusted odds ratios for all the independent variables.

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Anaphylaxis-induced hyperfibrinogenolysis and the risk of Kounis syndrome: the dual action of tryptase[☆]

To the Editor,

In the very interesting report published in the *Am J Emerg Med* [1], a young lady had anaphylaxis after a wasp sting, and despite abnormalities in coagulation cascade with markedly increased prothrombin time and activated partial thromboplastin, neither bleeding nor hepatic dysfunction was observed. The patient was discharged after treatment of anaphylaxis without administration of fresh-frozen plasma or antifibrinolytics such as tranexamic acid because the coagulation abnormalities were normalized spontaneously, and bleeding diathesis or thrombosis was absent. The authors thought that this unique case provides an interesting area of discussion.

Although biomarkers of myocardial necrosis and electrocardiographic changes were not given and allergic workup was not performed, tryptase levels were significantly elevated (initial level 200 µg/L). Therefore, in this patient, an abortive episode of type I variant of Kounis syndrome [2] cannot be excluded. The patient was treated with intravenous epinephrine. Indeed, epinephrine is the primary drug for anaphylaxis, but commercially available preparations of epinephrine contain sodium metabisulfite as a preservative, which is known to induce allergic reactions [3]. For this reason, currently, sulfide-free epinephrine preparations are available [4]. Insect stings can induce Kounis syndrome, which combines cardiac events with conditions associated with mast cell activation, involving interrelated and inter-

acting inflammatory cells and including allergic or hypersensitivity and anaphylactic or anaphylactoid insults.

Platelet activation and the ensuing coagulation cascade occur via stimulation of some known receptors on the platelet surface such as receptors for adenosine diphosphate, thromboxane, thrombin, serotonin, epinephrine, and some less-known receptors, which are associated with mast cell activation, such as receptors for histamine, high- and low-affinity immunoglobulin E receptors (Fcε RI and Fcε RII) and receptors for platelet-activating factor [5]. During activation, platelets change shape from discoid to spiculated form and release granules that contain proinflammatory (platelet factor 4, CD154 platelet-derived growth factor), prothrombotic (factor V, factor XI, platelet-activating inhibitor-1), adhesive (thrombospondin, fibrinogen, P selectin, von Willebrand factor), and aggregatory mediators (serotonin, Ca²⁺, Mg²⁺, ATP, ADP) [6]. However, mast cell mediators are also associated with fibrinogenolysis. For example, trypsin can degrade fibrinogen [7] and can activate prourokinase [8]. Chymase can inactivate thrombin [9]. Moreover, mast cells are a unique and important source of heparin, which does not exhibit fibrinolytic activity but prevents coagulation by acting as a cofactor of antithrombin III. However, heparin has been described as a potent cofactor of trypsin and of tissue-type plasminogen activator [10,11]. Recent data provide evidence that human tissue mast cells themselves are another important source of tissue plasminogen activator [12].

It is difficult to explain why anaphylaxis can be associated with either thrombotic or fibrinogenolytic events. Perhaps, mast cell clonality could explain this action, both thrombotic [2] and fibrinogenolytic [1], on the coagulation cascade

Table 1 Tryptase dual action

Thrombotic action [2]	Fibrinolytic action [1]
1. Activates the zymogen forms of metalloproteinases such as interstitial collagenase, gelatinase, and stromelysin and can promote plaque disruption or rupture	1. Cleaves the α and especially β chain of fibrinogen, which regulate the removal of the thrombin cleavage site and the critical polymerization site, resulting in inhibition of clot formation
2. Degrades the pericellular matrix components fibronectin and vitronectin and neuropeptides, such as vasoactive intestinal peptide and calcitonin gene-related peptide	2. Degrades procoagulant proteins, which prevent fibrin deposition
3. Activates neighboring cells by cleaving and activating protease-activated receptor-2 and thrombin receptors	3. Activates the single-chain urinary plasminogen activator (or prourokinase) and converts plasminogen into plasmin, which degrades fibrinogen and other coagulation factors
4. Degrades high-density lipoprotein	

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(Table 1). Indeed, activating mutations were recently found in *c-kit*, which codes for KIT, the receptor for stem cell factor, which is essential for mast cell development, proliferation, survival, adhesion, and homing [13]. We postulate that these events result in hyperresponsive mast cell phenotype with increased release of mast cell tryptase and other inflammatory mediators that are able to induce Kounis syndrome and differentiate mast cell content. This could also explain why few patients develop chest pain with/or electrocardiographic changes during allergic, hypersensitivity, anaphylactic, or anaphylactoid episodes. We believe that further studies are necessary to clarify the important role of mast cells in endogenous thrombolysis and coagulation cascade. We agree with the authors that, in any case of anaphylaxis, coagulation assessment should always be performed.

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Acute appendicitis: emergency medicine physician and surgeon clinical judgment vs abdominal computed tomography scan

To the Editor,

We read, with great interest, the article by Jo et al [1], "The accuracy of emergency medicine and surgical residents in the diagnosis of acute appendicitis," which states that, in patients with right lower quadrant abdominal pain who have already been evaluated by an emergency medicine resident, consultation evaluation by a surgical resident does not appear to improve clinical diagnostic accuracy, and routine performance of computed tomography (CT) before surgical consultation should be considered for these patients [1]. Although we agree with the authors that CT scanning is a useful option for detection or ruling out of acute appendicitis, in patients who have typical findings in history and physical examination, routine CT is not a necessary option, and early consultation with surgical resident will reduce the preoperative time and also avoids the patient from radiation exposure and cost of unnecessary CT scan. Indeed, we want to emphasize that even the best imaging modalities can never replace the clinical judgment of an experienced surgeon or emergency medicine physician.

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