

Review

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Review

An Insight into Kounis Syndrome: Bridging Clinical Knowledges with Forensic Perspectives

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Abstract: The Kounis syndrome (KS) is an acute coronary syndrome triggered by allergic or hypersensitivity reactions. Incidence rates vary, with studies reporting 19.4 per 100.000 among all admissions and 3.4% among allergy patients. This review explores the expanding understanding of KS, encompassing various manifestations, and focusing on both clinical data and forensic findings useful in performing the diagnosis. The pathophysiology of this syndrome involves a complex interplay between allergic reactions and the cardiovascular system. Mast cell activation, histamine release, leukotrienes, cytokines, and platelet activation can contribute to the coronary events. A classification system with three types (Allergic Angina, Allergic Myocardial Infarction, Allergic Stent Thrombosis) aids in categorizing presentations. The diagnosis of KS relies on clinical presentation, laboratory findings and imaging. Post mortem assessment of KS is based on the integration of circumstantial data, autopsy and histological findings. Biochemical and immunohistochemical analyses also contribute to post-mortem diagnosis. In conclusion, a combined, multidisciplinary approach, should be gained to ease diagnostic process which is crucial for forensic practitioners in confirming KS occurrence.

Keywords: Kounis syndrome; anaphylaxis; postmortem; immunohistochemistry; biochemistry; tryptase; acute coronary syndrome

1. Introduction

The Kounis syndrome (KS) is an acute coronary syndrome that occurs in the setting of allergic or hypersensitivity reactions, firstly described by Nicholas Kounis [1,2]. It encompasses a spectrum of allergic reactions leading to acute coronary events. The mechanism involves the release of inflammatory mediators during an allergic response, which can trigger coronary artery spasm or plaque rupture, leading to angina or myocardial infarction. The first two cases are presented by Kounis and Zavras [1], who reported symptoms of angina-like chest pain and electrocardiographic changes during allergic reactions. The symptoms were initially attributed to coronary artery spasm triggered by an allergic response. Since its first discovery, more and more cases have been reported in the medical literature. The disease mechanisms have been further analysed, expanding the definition of KS to not only a single-organ disease but a complex multisystem disease [3], which includes any coronary syndrome related to mast cell-associated disorders and inflammatory cell interactions, such as allergic angina, allergic myocardial infarction, and allergic stent thrombosis and

all their implications. Moreover, some work has been done to generate a classification and subdivision of the disease in three subtypes to facilitate diagnosis and treatment [4–6].

As depicted in a recent study [7], the interplay between anaphylaxis and KS is quite complex, and it can involve the skin, respiratory, and cardiovascular systems. This significantly influences both morbidity and mortality, calling for bigger population studies, case reports and appropriate management plans.

The aim of this review is to analyse the epidemiological and pathophysiological aspects of the KS, both to provide an insight of the disease and to describe the main literature data regarding the forensic tools for an appropriate postmortem assessment.

2. Epidemiology and Pathophysiology

KS is considered a relatively rare condition, and its true prevalence is not well-established due to under-recognition and under-reporting [6].

Recent reports suggest that KS has been observed across all races, age groups (2 to 90 years old), and geographic locations. It has been mostly reported in southern Europe, particularly in Turkey, Greece, Italy, and Spain [6]. The geographical variation may be attributed to physician awareness, climate, environmental conditions, overconsumption of medicines, or inadequate preventative measures. An example is the district of Achaia, Greece, where 52 cases were reported in the last 4 years, resulting in an estimated annual incidence of 4.33 cases per 100,000 inhabitants [6].

In a prospective study lead by Akoz et al. [8], it was found that out of 138.911 patients admitted to the emergency department in one year, 793 presented with allergy complaints. The incidence of KS among all admissions and allergy patients was 19.4 per 100,000 (27/138.911) and 3.4% (27/793), respectively.

Between 2010 and 2014, 51 cases of KS have been reported to the International Pharmacovigilance Agency, with almost half in 2014 [9].

In a retrospective study lead in the Swiss Canton [10], the incidence of anaphylaxis with circulatory symptoms was estimated over a 3-year period, revealing 246 episodes in 226 individuals, with an incidence of 7.9–9.6 per 100.000 inhabitants per year. The case–fatality rate was 0.0001%, with three reported deaths.

Various causes can trigger KS, such as foods, medications (i.e., antibiotics, nonsteroidal anti-inflammatory drugs, contrast media), environmental factors, including insect bites [6,9,10] (Figure 1). The pathophysiology of KS involves a complex interplay between allergic or hypersensitivity reactions and the cardiovascular system. The syndrome is characterized by the activation of inflammatory mediators during an allergic response, leading to coronary artery spasm or, in some cases, plaque rupture [6]. The key aspects include mast cell activation, histamine release, inflammatory response caused by leukotrienes and cytokines, platelet activation, endothelial dysfunction [6]. KS can manifest in various ways, ranging from angina to acute myocardial infarction. The specific presentation may depend on factors such as the type and severity of the allergic reaction, individual patient characteristics, and the presence of pre-existing cardiovascular conditions [6].

Understanding the pathophysiology of KS is crucial for an appropriate diagnosis and management. Treatment often involves addressing the underlying allergic reaction, managing coronary artery spasm, and providing supportive care for cardiovascular events. To facilitate this, a classification system for the KS has been provided [4,6]. Of the three existent types, each one presents different pathophysiology characteristics and clinical assessment, but there can be an overlap between the types, so individual cases may not fit into one specific category. It is important to note that these classifications provide a framework for understanding the different clinical scenarios associated with KS [6,11]. Type I variant, also known as vasospastic allergic angina, usually develops in subjects with no atherosclerotic phenomena in coronary arteries and with no other risk factors, manifesting itself with endothelial dysfunction or microvascular angina: the releasing of the inflammatory mediators typical of anaphylaxis could cause et coronary spasm with no cardiac enzyme alterations, et myocardial infarction, leading to death in the most severe cases [6,11]. Type II variant is instead an allergic acute myocardial ischemia which develops in subjects suffering from

coronary atherosclerosis: the release of inflammatory mediators can determine transient events characterized by coronary spasms with normal cardiac enzymes up to rupture of plaques and death [6,11]. Lastly, the type III variant occurs in patients with coronary stents, at which occur thrombotic phenomena secondary to the onset of the anaphylactic phlogistic phenomena. In these cases, it is possible to detect eosinophils and mast cells on histological examination performed after autopsy [6,11]. The three main types are reported in Figure 1. These classifications help in understanding the diverse ways in which the syndrome can manifest, and therefore can be treated.

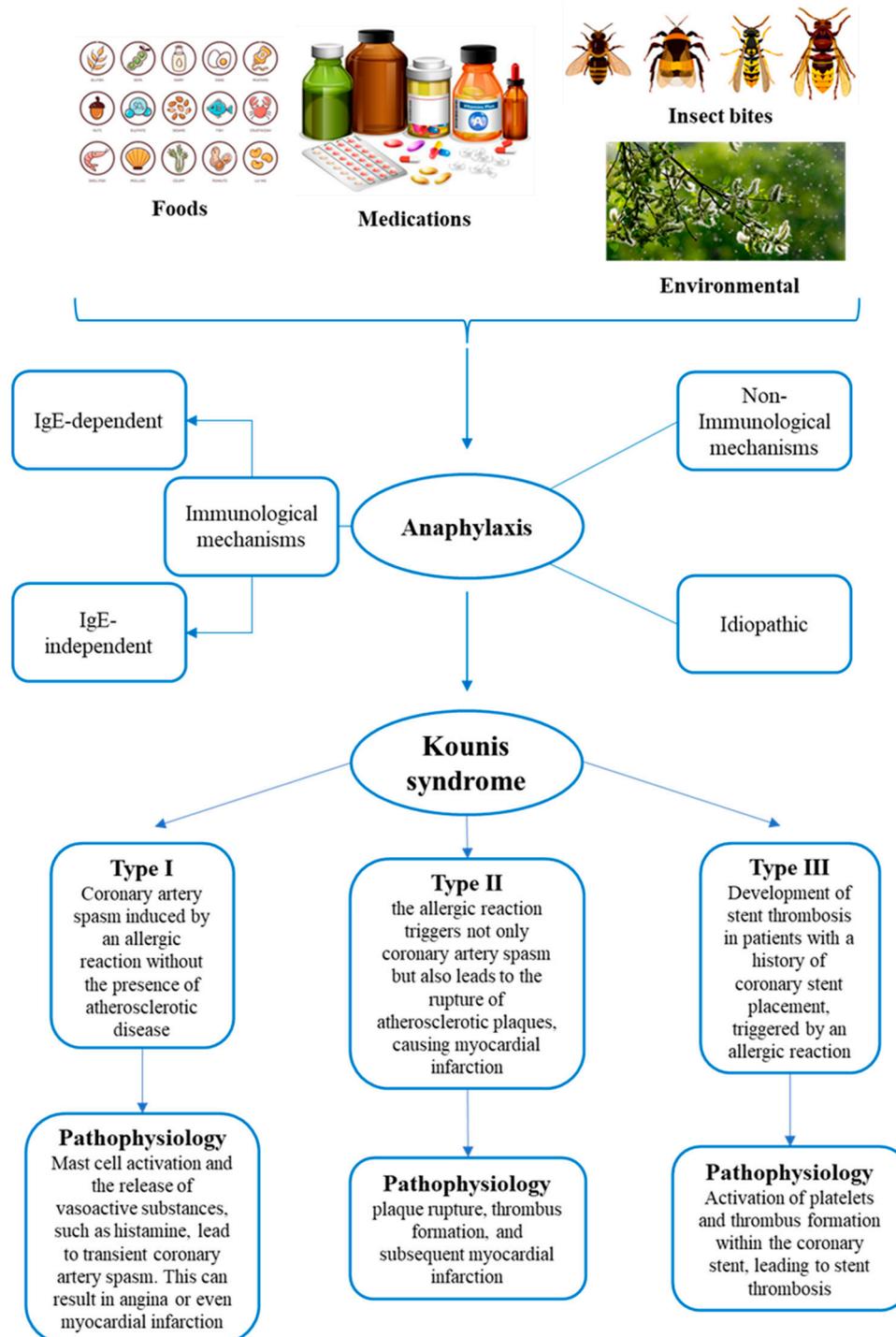


Figure 1. Summary of the main triggering factors of anaphylaxis, pathophysiological mechanisms of anaphylaxis and types of Kounis syndrome.

3. Clinical presentation

KS is a complex multisystem disease related to allergy-hypersensitivity that affects the skin, respiratory, and cardiovascular systems, involving not only the coronary arteries but also the cerebral and mesenteric ones [3,6]. As there are no specific findings of KS, the evaluation of the patient's clinical history can help to identify the etiological and clinical correlation between any allergic triggering factors and the onset of acute coronary syndrome [11]. Risk factors include atopic susceptibility with previous allergic episodes, hypertension, smoking, diabetes, and hyperlipidemia [12].

Clinically, KS manifests as a combination of an acute, subacute, or chronic allergic reaction (usually anaphylaxis) simultaneously associated with cardiac symptoms, including chest pain, dyspnea, chest discomfort, palpitation, tachycardia or bradycardia, pulmonary oedema, coronary vasospasm, angina pectoris, myocardial infarction, and acute heart failure [12,13]. In most cases (80%), symptoms appear within an hour of exposure to the allergen, although in 9,2% a later onset is possible, after more than 6 hours [12]. Regarding cardiac involvement, the most common symptoms and signs are chest pain (60%) and hypotension (75%), due to distributive shock, related to extensive peripheral vasodilation, and cardiogenic shock with suppression of myocardial function [14,15]; it is also possible to observe dermatological (70%), respiratory (30%) and gastrointestinal (20%) symptoms [13,14]. Dermatological manifestations, such as urticaria, rash, erythema, and angioedema, representing classic findings in case of allergic reaction/anaphylaxis, can be useful for the diagnosis of KS, although they may be absent or delayed. However, the absence of cutaneous manifestations is not a criterion for excluding KS, but rather a sign of severe cardiogenic and distributive shock: during anaphylaxis, cardiac collapse, determining a marked reduction in cardiac output with vasoconstriction and hypotension, can drastically reduce venous return and delay the action of anaphylactic mediators at the skin level [16]. Common symptoms and signs related to the allergic/anaphylactic reaction and in KS also include general malaise, nausea, vomiting, fainting, diaphoresis, cold extremities, paleness, palpitations [13,16].

Furthermore, reduced cerebral perfusion related to an anaphylactic reaction can cause neurological symptoms such as headache, tiredness, drowsiness or altered neurological status, which are frequently considered not noteworthy because of their poor specificity, and so lead to KS misdiagnosis. [16]. The consequences of post-allergic coronary syndrome, or cardiac anaphylaxis, may be myocardial ischemia, acute myocardial infarction, conduction defects, malignant arrhythmias (i.e., ventricular fibrillation), cardiac muscle cell dysfunction, and, in the absence of treatment, cardiorespiratory arrest or sudden cardiac death. [11].

4. Clinical diagnosis

The diagnosis of KS is based on clinical presentation, laboratory findings, ECG, echocardiography, and coronary angiogram [3,6,7,12,16]. In patients with symptoms and/or signs of systemic allergic reactions, especially if associated with cardiac symptoms, it is necessary to examine electrocardiographic findings and measure troponin levels to exclude or confirm the diagnosis of KS [6,12].

Measuring serum tryptase, IgE antibodies, histamine, cardiac enzymes (i.e., CK and CK-MB) and cardiac troponins are particularly helpful to better define the diagnosis of KS [16]. Serum tryptase represents an indicator of mast cell activation [17] and its levels begin to increase already 30 minutes after the onset of the signs and symptoms of the allergic reaction, reaching their peak during the following 2 hours [3,6,16]. In clinical practice, the value of serum tryptase concentration indicating anaphylaxis must be higher than 11.4 ng/mL, which has a sensitivity of 73% and a specificity of 98%; furthermore, due to the short half-life (about 90 minutes) [6,14], serial dosing with a minimum of three determinations is recommended [11]. Histamine is rapidly released from mast cells and remains in circulation for only about 8 minutes after an allergic event, thus it is recommended to collect blood samples immediately after the onset of chest pain [3,6]. Cardiac enzymes are directly correlated to the severity of the anaphylactic reaction and their increase is marker of cardiac damage [11]. Particularly, the CK and CK-MB and cardiac troponins increasing support the main involvement of both coronary arteries and/or heart during anaphylaxis [3,13,16]. Indeed, in case of anaphylaxis,

angioedema, urticaria and urticaria-angioedema, the troponin I levels resulted higher compared either to healthy patients [13,16] and to those with milder allergic reactions [3]. For this reason, these enzymes should be dosed to promptly identify the heart damage attributable to KS to provide a quick management [6].

The acute release of inflammatory mediators in type I can provoke coronary artery spasm without an increase in cardiac enzymes or can determine coronary artery spasm up to acute myocardial infarction with raised cardiac biomarkers. Similar findings are described for type II, in which it is possible to detect either coronary spasm associated with normal levels of cardiac biomarkers, or signs of plaque erosion or rupture responsible for acute myocardial infarction, determining the increasing of cardiac biomarkers [3,14].

The KS diagnosis is performed also by electrocardiogram (ECG) echocardiogram and a coronary angiography [3,14].

ECG in KS shows as most common finding the ST segment elevation in the anterior and inferior leads, related to vasospasm of the right coronary artery, which is the most frequently vessel involved. It is also possible to detect findings of heart block and cardiac arrhythmias of any degree. In patients affected by type I of KS, in which cardiac enzymes and coronary angiography may be normal and any electrocardiographic abnormalities are transient, it is essential that ECG monitoring is repeated several times, to identify the KS early and promptly [11,14,16]. Cases may also occur with normal or non-specific ECG: if no elevation or depression (existing or transient) of the ST segment, no inversion of the T wave, flat or pseudo-normalization of the T waves are detected reperfusion surgery may be delayed [14].

Echocardiography and coronary angiography allow to detect cardiac wall abnormalities and define the anatomy of the coronary arteries [6]. The echocardiogram integrates the information given by the ECG providing data about abnormal movement of the cardiac wall normally supplied by the coronary artery involved in the disease [14]. Angiography is the main investigation for the assessment of the cause of coronary abnormality because of it can establish whether the obstruction to coronary flow is due to vasospasm or thrombosis, thus representing a useful tool for the differential diagnosis between the three KS variant. [11,13].

Newer techniques such as single photon emission computed tomography (SPECT) with thallium-201 and SPECT with 125I-15-(p-iodophenyl)-3-(R, S) methylpentadecanoic acid (BMIPP), in conjunction with Cardiac Magnetic Resonance Imaging are useful to better define the actual cardiac damage, especially when in the type I variant of KS the coronary angiography is found to be normal [3,7]. Cardiac SPECT and cardiac MRI have proven effective both for revealing severe myocardial ischemia and subendothelial damage, and for distinguishing KS from myocarditis (although the differential diagnosis is histological) [13,16]. On dynamic cardiac magnetic resonance imaging (MRI), delayed contrast-enhanced images show normal washout in the subendocardial lesion in patients with variant KS type I [6,7].

5. Post mortem assessment of Kounis syndrome

Postmortem assessment of anaphylactic death is considered a challenge because of evidence emerging from autopsy and histology is not pathognomonic. The diagnosis should be based on the integration of circumstantial and anamnestic data, autopsies, histological findings, biochemical and immunohistochemical data [18–20].

The gross and microscopic findings at respiratory system, such as laryngeal edema, tracheo-bronchial hypersecretion, bronchoconstriction, emphysema and acute pulmonary edema, congestion, and intra-alveolar hemorrhage, can support the occurrence of anaphylaxis [19], but some of these findings can be absent or not specific. Moreover, if KS is suspected, histological examination of the heart and coronary arteries is strongly recommended. For this purpose, the use of different histological stains can highlight the presence of different inflammatory cells involved in allergic reaction. In fact, eosinophils and mast cells infiltrates are identified using hematoxylin-eosin and Giemsa (or toluidine blue) staining, respectively [21,22]. In cases of KS manifesting as coronary spasm, a high presence of mast cells has been found in the coronary arteries wall, including the area

of spasm, especially in the tunica adventitia [22–25]. Furthermore, many studies report that the major count of mast cells is concentrated in atherosclerotic and hemorrhagic plaques [21,22]. Histologically, myocardial alterations caused by the ischemic insult related to the compromise of coronaries due to the heart anaphylactic involvement can be observed. In fact, when death occurs within a short period of time from the ischemia onset, it is possible to find signs such as myofiber eosinophilia, elongation of sarcomeres and nuclei, wavy fibers, interstitial oedema, and contraction band, suggesting the occurrence of a so-called early myocardial ischemia [26,27]. Kitulwatte et al. reported the presence of transmural contraction band necrosis together with consistent inflammatory cells infiltrates [19].

However, since these findings cannot be considered pathognomonic, other analyses, such as biochemistry and immunohistochemistry, can contribute to perform the postmortem diagnosis of anaphylaxis and KS [18].

Particularly, concerning blood biochemical investigations, many studies have focused on serum tryptase and IgE evaluation. Serum tryptase is the most used biomarker of anaphylaxis and is a very stable enzyme, being detectable up to 6 days after death [18,20]. However, since post-mortem degradation processes can lead to a reduction in the effective concentration of tryptase as the post-mortem interval (PMI) increases, in case of suspected anaphylactic death, it is suggested to take a blood sample as soon as possible [18]. Various cut-offs for serum tryptase levels from peripheral blood have been reported in the forensic literature. As reported by Kounis et al. [20] a level of tryptase of 10 µg/L or greater has a sensitivity of 86% and specificity of 88% for the diagnosis of postmortem anaphylaxis. Tse et al. and Edston et al. proposed a tryptase cut-off value ≥ 53.8 µg/L and 45 µg/L on femoral blood, respectively. The latter one can be considered as a new limit value [28,29]. However, if blood is collected from central vessels, such as the aorta, the suggested threshold value is 110 µg/L [30], higher than the previous ones, since some factors, such as prolonged cardiac massage or defibrillation, are responsible for an increase in mast cell degranulation and in tryptase levels, due to visceral trauma from chest compressions [31]. Therefore, peripheral blood is preferable to central blood for post-mortem tryptase determination [32,33]. However, even in the case of peripheral blood, in forensic practice, it is necessary to highlight that some factors can influence the tryptase concentration (i.e., hemolysis and duration of the agonal period). Furthermore, increased tryptase levels have also been described in non-anaphylactic deaths [19,20], such as sudden infant death syndrome, acute deaths after heroin injection, traumatic deaths, and asphyxia.

Total and specific IgE assayed in postmortem serum can only verify atopic disposition and the degree of sensitization to a particular allergen [18,19]. Nevertheless, integrating the results of these analyzes with serum tryptase levels can still provide useful information on the cause of death. In suspicion of KS, is important to measure the levels of anaphylaxis-related substances such as carboxypeptidase A and histamine in the pericardial fluid and pericardial tissue, as well as the levels of specific IgE in the pericardial and cerebrospinal fluids. Specifically, an increased concentration of carboxypeptidase A, secreted by mast cells, was found in both postmortem serum and pericardial fluid of subjects who died from anaphylaxis [20].

Since KS can cause coronary vasospasm up to early myocardial ischemia or infarction, a further useful biochemical investigation consists in the measurement of serum troponin I levels to evaluate cardiac damage and to support post-mortem diagnosis of KS [34].

Immunohistochemistry is another investigation useful for postmortem diagnosis of anaphylaxis, although it is important to underline that the identification of mast cells in the tissues cannot be considered sufficient to make a diagnosis of certainty. Indeed, increased number of mast cells can be detected also in various biological processes (i.e., tissue remodeling, angiogenesis, fibrosis, and asphyxia) and in non-anaphylactic deaths. The main effectors of inflammation during anaphylaxis, i.e., eosinophils, basophils but above all mast cells, have been found in tissues, as bronchial, respiratory, and intestinal mucosa, and the red pulp of the spleen and connective tissue (i.e., cutaneous, and perivascular) [18,22,25]. When a suspicion of KS raises, it is fundamental to search possible infiltrates of inflammatory cells released during anaphylaxis, such as eosinophils and mast cells in myocardial tissue and coronary arteries [20]. Increased numbers of mast cells in the three

layers of the coronary arteries and myocardial cellular infiltrates of neutrophils with mast cells and eosinophils have been detected in patients died because of coronary spasm. Therefore, during anaphylaxis, may also be involved the pericardial tissue, in which histological examination has revealed perivascular areas of infiltration of lymphocytes, macrophages, neutrophils and mast cells [7,20]. These findings suggest that, in KS, the myocardial damage seems related to the effect of both mast-cell degranulation and the release of inflammatory mediators that affect the cardiovascular system (i.e., coronary vasoconstriction induced by histamine). Thus, the diagnosis should be performed using the immunohistochemical evaluation of degranulated tryptase in coronary walls and myocardial tissue [18,30]. Moreover, some studies also reported the analysis of chymase, representing other marker for mast cells detection [30,35].

A schematic summary of the main investigations to reach the post mortem diagnosis of Kounis syndrome is reported in Figure 2.

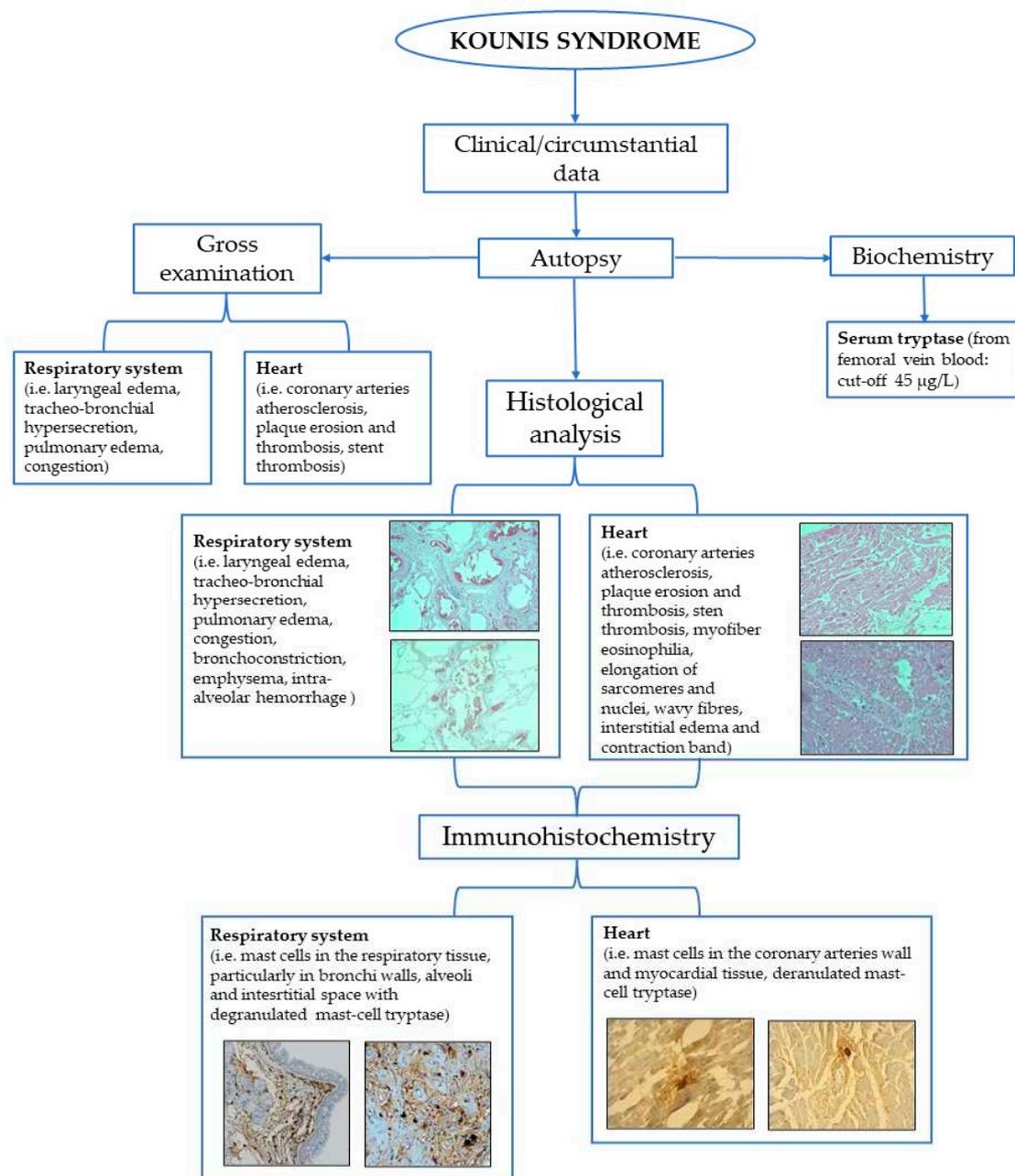


Figure 2. Flow-chart of the main tools for post mortem assessment of Kounis syndrome.

6. Conclusion

Kounis syndrome, also known as allergic myocardial infarction or allergic angina syndrome, is characterized by the combination of an allergic/anaphylactic reaction, with release of specific inflammatory mediators, and acute coronary syndrome, with ischemic myocardial damage. Even if the clinical diagnosis of KS is already established using several laboratory and instrumental investigations, the post-mortem diagnosis is a challenge for pathologist.

KS assessment in the forensic setting requires the integration of clinical/anamnestic data with the findings belonging from multiple investigations. Firstly, the heart macroscopic examination provides information on the coronary arteries; the histological examination of myocardium and coronary arteries can reveal inflammatory infiltrates, such as mast cells and eosinophils. Biochemical and immunohistochemical analyses may offer significant data. Biochemical investigation for inflammatory mediators (i.e., histamine, tryptase, total and specific IgE) can reveal increased values suggesting an anaphylactic reaction; on the other hand, the troponin I represent a marker for acute myocardial damage. Then, immunohistochemistry integrates previous investigations to ascertain the mast cell infiltrate and above all the presence of degranulated tryptase at coronary arteries supporting the KS occurrence.

In conclusion, even if the forensic evidence lack of a standardized diagnostic model to assess the KS occurrence, the implementation of a multiparametric approach can help the pathologist in the forensic practice.

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