



Letter to the Editor

Postmortem diagnosis of drug-induced anaphylactic death: Kounis syndrome and hypersensitivity myocarditis are the likely culprit in death of severe anaphylactic reactions



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Kounis syndrome¹ combines acute coronary syndromes with conditions associated with mast cell activation, involving interleukin and interacting inflammatory cells, and includes anaphylactic or anaphylactoid and allergic or hypersensitivity insults. It is caused by preformed and newly synthesized inflammatory mediators released during the anaphylactic process.² A subset of platelets bearing FCεRI and FCεRII receptors are also involved in the activation cascade.²

Three variants of Kounis syndrome have been described so far³: In type I variant, coronary spasm in normal or nearly normal coronary arteries, associated with anaphylactic reaction can progress to myocardial infarction. In type II variant culprit but quiescent pre-existing atherosclerotic disease combined with anaphylactic reaction can result in acute myocardial infarction. In type III variant, hypersensitivity to any implanted intracoronary stent components can result in devastating intrastent thrombosis.

Hypersensitivity myocarditis is an inflammatory disease affecting the myocardial tissue and the cardiac conduction system manifesting mainly as a complication of drug therapy.⁴ The only histological differences between the above 2 hypersensitivity conditions are that in hypersensitivity myocarditis there is presence of eosinophils, atypical lymphocytes and giant cells in myocardial biopsy, whereas in Kounis syndrome these inflammatory cells are present in coronary intima, media and adventitia.³

In the very important paper published recently in this Journal,⁵ the authors reported on a 55-year-old Caucasian woman who was found dead following clarithromycin administration for bacterial bronchitis 2 h previously. On autopsy, which took place 60 h after death, the heart was found normal and the coronary arteries have had mild atherosclerotic disease. Eosinophils and mast cells were present, on spleen histology and mast cell tryptase was present in aortic, femoral and right heart blood serum suggesting anaphylactic death.

This report raises important questions concerning the anaphylactic death and histological procedures undertaken in order to elucidate the cause of death and the manner of death. Mast cell and eosinophilic tissue infiltration ensues from multiple etiologic factors and associations including medications, infectious agents or organisms, malignant neoplasms, and chemicals that stimulate the immune system. A number of disease entities are in the differential list and these include hypereosinophilic syndrome, hypersensitivity drug reactions, asthmatic bronchitis, and parasitic and fungal infections. In addition, organ/tissue-specific or systemic diseases such as Kounis syndrome, hypersensitivity drug-induced myocarditis, Churg-Strauss syndrome, Wegener granulomatosis, microscopic polyangiitis, and Goodpasture syndrome are also included because they have overlapping clinicopathologic characteristics.⁶

In the described case,⁵ sudden death have had occurred following clarithromycin administration, and the authors correctly suspected anaphylactic death based on findings in spleen histology and blood serum tryptase. However, the heart and especially the coronary arteries should be regarded as main organs, and primary target of anaphylaxis,⁷ serving as a primary door through which life crosses to death and should be scrutinized in any postmortem examination.

Kounis syndrome manifesting as coronary spasm can lead to sudden death from lethal cardiac arrhythmias with coronary arteries infiltrated by mast cells.⁸ Drug-eluting stent thrombosis, that is usually a manifestation of Kounis syndrome, is attributed to stent components of nickel, polymer and the eluted drugs that can act as antigenic complex inside the coronary arteries.⁹ Histological examination of coronary artery and Giemsa stain for mast cells with positive control has shown scattered mast cells in the tunica adventitia.¹⁰

Drug-induced hypersensitivity myocarditis is a disease that can lead to sudden death¹¹ with myocardial tissue infiltrated by eosinophils and mast cells and there are reports of sudden cardiac death from macrolides including azithromycin.¹²

Therefore, pathologists should have in mind all above pathologies and should perform histologic examination of the myocardium and especially of coronary arteries that could reveal the presence of inflammatory cells such as mast cells and eosinophils. This would help in elucidating the cause of sudden death and in particular the manner of death.

Conflict of interest

No conflict of interest.

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