C1 esterase inhibitor deficiency – A rare cause of coronary artery thrombosis

Dr. M. Abela MD, Dr. R. Cacha MD, Dr. E. Gerada MD, Prof. S. Montefort MD, Dr. A. Cassar MD
Mater Dei Hospital, Malta.

Abstract
C1 esterase inhibitor (C1-INH) is a serine protease inhibitor that acts on a number of proteins that play a role in the complement, coagulation and kinin-kallikrein cascades. By adhering to specific targets (C1, Factor XIIa, MASP-1, MASP-2, Kallikrein), it helps maintain a balance between thrombin generation and fibrinolysis.

Deficient patients however exhibit an elevated thrombotic risk in response to unregulated complement activation and fibrin formation.

Case report
This case report describes the history of a middle-aged gentleman, known to have familial C1-INH deficiency, suffering an acute coronary artery thrombosis, complicated by deep vein thrombosis (DVT). The diagnosis of familial C1-INH deficiency was made in his teenage years after presenting to hospital with recurrent episodes of umbilical, abdominal pain and periumbilical tenderness which were resistant to treatment with both anti-histamines and non-steroidal anti-inflammatory drugs. Tests were consistent with a quantitative deficiency of C1-INH, classical type of type I hereditary angioedema.

The patient then presented to the emergency department at the age of thirty complaining of a fifteen minute episode of severe central compressive chest pain at rest. This was associated with diaphoresis and vomiting. An acute coronary syndrome (ACS) event had to be excluded. Electrocardiography and echocardiography did not show any features suggestive of a myocardial infarction. However, a high troponin 1 of 0.4ng/ml rising to 3.6ng/ml in five hours from symptom onset prompted the caring physician to treat as an non-ST segment elevation myocardial infarction (NSTEMI) with Opioid, intravenous heparin and nitrates. Aspirin was omitted because of a known augmented risk of aspirin-related angioedema in individuals with C1-INH deficiency. An urgent intravenous angiography was performed by the cardiologists. This revealed a right coronary artery filling defect in the middle segment, consistent with intracoronary thrombus rather than rupture of an atherosclerotic plaque (Figure 1). His stay at coronary care unit complicated with DVT of the right and left lower limb, despite adequate anticoagulation with intravenous heparin.

He was started on long term warfarin as prophylaxis for future thrombotic events. To date, he remains well without any further coronary arterial or venous thrombotic events. A repeat ECHO, six months after this event, showed normal left ventricular function and good ejection fraction. He still requires high doses of perampanel C1-INH at least twice a month.

Discussion
C1-INH deficiency, contributing towards a pro-thrombotic state as a result of complement over-activation. (Figure 2.)

In C1-INH deficiency, over-activation of the complement pathways in turn attenuates cardiovascular risk. The benefits of C1-INH as an experimental therapeutic agent has also helped demonstrate its role in reducing the extent of myocardial ischaemia, possibly by direct influence on neutrophil-mediated ischaemia-reperfusion injury.

In patients undergoing aortic valve endarterectomy, low levels of C1-INH in patients with an intact lesion pathway seems to predict earlier re-endothelialization as they are unable to mediate complement activation, suggesting that C1-INH has an important role to play in atherosclerosis.

Conclusion
We hypothesize that uncontrolled complement activation with insufficient regulation of the lesion pathway (resulting in higher levels of factor XIIa, C1s, MASP-1 and Kallikrein) as a result of C1-INH deficiency, are the main reasons for the elevated thrombotic risk in such patients. Inhibiting these innate proteases should protect against myocardial infarction and reperfusion injury, primarily by restoring balance between thrombosis and inflammation.

Figure 1. Intracoronary angiogram illustrating a mid right coronary thrombus (A & B) with a normal left coronary circulation (C).

Figure 2. C1 Inhibitor's role in the coagulation cascade.

References

