

CHOLESTEROL CRYSTAL EMBOLIZATION IN A SAUDI PATIENT AFTER CARDIAC SURGERY

- A Case Report -

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Summary

An eroded atheromatous aorta may be a source of cholesterol crystal embolism(CCE). Embolization of atheromatous material accounts for obstruction of distal arterioles around which a foreign-body giant cell granuloma inflammatory reaction develops. The diagnosis is often delayed or un recognized because of varying or misleading clinical signs, such as renal insufficiency, digestive or neurological symptoms, or both or unexplained multiple-system disease.

Although CCE can occur spontaneously, it has been increasingly recognized as an iatrogenic complication from an invasive vascular procedure, such as manipulation of the aorta during angiography or vascular surgery. It has also been reported to occur following anticoagulant therapy or thrombolysis.

Patients undergoing coronary artery bypass grafting (CABG) often experience a combination of these factors: anticoagulation, intra-arterial angiographic procedures and intraoperative aortic cross-clamping. These multiple factors could account for the acute and severe postoperative clinical and biological findings observed in the case reported here.

A 65-year-old Saudi man was admitted to our hospital on July 9, 2008 due to chest pain at rest. He had suffered from type 2 diabetes mellitus on Oral hypoglycemics, hypertension on treatment, impaired renal functions and hypercholesterolemia, he was an ex-smoker with history of diagnosed pulmonary interstitial fibrosis.

He had Coronary angiography in another hospital on May 2008 showing a left main lesion 60%, Left anterior descending lesion 90%, circumflex lesion 80% and Right coronary lesion 70%, three weeks later an acute on top of chronic deterioration in renal chemistry was observed for which conservative treatment was chosen.

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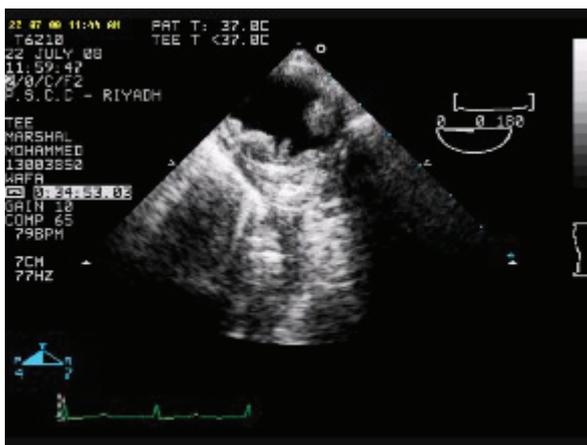
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Coronary artery bypass grafting (CABG) was decided, with preoperative optimization by haemodialysis and pulmonologist consultation which required CT chest and pulmonary function tests confirming interstitial lung disease with moderate to severe lung restriction. The preoperative management plan included continuous infusion of heparin and glyceryl trinitrate, aspirin and beta blockers.

On the night before surgery the patient was having chest pain at rest with depressed ST changes in spite of previous treatment, he was hemodynamically stable, oliguric, having palpable peripheral pulses and normal bowel habits.

Fig. 1

intraoperative TEE showing multiple atheromatous plaques protruding in the lumen of descending thoracic aorta > 5 mm, with one of them freely mobile.



Considering the patient's condition and intraoperative risks Intra-aortic Balloon Pump (IABP) was inserted in the operating room before induction of anesthesia under local anaesthesia and sedation, after stable induction of anesthesia, TEE examination showed mildly impaired ventricular systolic functions with a surprisingly multiple atheromatous plaques protruding in the arch and the ascending parts of aorta, with one mobile plaque in the distal arch. This new information about the nature of the aortic wall lead the cardiac team to shift from on pump surgery to off pump coronary bypass to minimize the aortic manipulation. Apart from that, the procedure was uneventful, the patient was shifted to intensive care with stable hemodynamics on Inotropic support.

On the first post operative day ischemic changes

appeared in lower limbs; there was bilateral blue discoloration of feet with good pulsations, there were ischemic patches and purpura in both lower limbs as well. the IABP was removed, however the changes continued and progressed into the left leg, the Doppler always showed intact flow in spite of these changes.

Fig. 2

skin manifestations in CCE, early signs include blue toes, levido reticularis, late signs include extensive skin ischemia and necrosis.



On the second post operative day the patient developed abdominal distension with tenderness, there was minimal blood stained stool as well, CT abdomen revealed chronic infrarenal aortic aneurysm, Doppler study of mesenteric vessels showed patent large mesenteric arteries. Additionally renal function was deteriorating and required dialysis.

The differential diagnosis of cholesterol crystal embolism was considered, anticoagulant treatment was stopped, CBC did not show Eosinophilia and CRP was elevated up to 91. The patient was kept ventilated, on inotropes and dialysis, with conservative treatment of his vascular and abdominal conditions. On the ninth post operative day the conscious level deteriorated and CT brain showed acute multiple infarctions. After 20 days in the intensive care unit, the patient died with multiple organ failure and septic shock.

Discussion

Cholesterol crystal embolization (CCE) was first identified by Panum in 1862¹, However little was known about this syndrome. After the experimental work carried out by Flory² and Snyder and Shaprino,

Embolic migration of cholesterol has been commonly accepted. It is a systemic disorder due to embolization of cholesterol crystals from atherosclerotic plaques in the aorta and major branches. Although it can occur spontaneously³, it is increasingly being recognized as an iatrogenic complication from an invasive vascular procedure⁴⁻⁷.

CCE occurs in patients with diffuse atherosclerosis and multiple vascular risk factors; in the largest review to date, Fine et al⁸ discussed the findings in 221 cases of CCE. Notable patient characteristics included a mean age of 66 years and a male-to-female ratio of approximately 3 to 1. More than half the patients had a history of hypertension, more than one third had a history of atherosclerotic disease, one third had a history of renal failure, and slightly more than 10% had diabetes mellitus.

Those high risk patients develop CCE when they are exposed to a triggering factor⁹. Such triggering factors include angiography, aortic and cardiac surgery, anticoagulant therapy and thrombolytic therapy¹⁰.

In the literature, one study of a total of 1,786 consecutive patients 40 years of age and older, who underwent left-heart catheterization, showed that (1.4%) were diagnosed as having CEE¹¹, other reviews showed that angiographic procedures accounted for 50% of cases of CCE, with Aortic surgery responsible for 18% of published cases^{8,12}.

Once atheromatous plaques become denuded of their endothelial lining, the underlying extracellular cholesterol-rich matrix is allowed free access to the arterial circulation and subsequently becomes lodged in distal capillaries and small arterioles¹³. Its presence in vascular lumens elicits a local inflammatory response and occasionally an eosinophilic infiltrate. Within 48 h, a foreign-body giant cell reaction often occurs^{13, 14} resulting in the engulfment of the cholesterol crystals.¹⁴ Subsequently, endothelial proliferation and intravascular thrombosis and fibrosis occur^{15, 16}. CCE also provokes a systemic inflammatory component manifested by fever, myalgia, and weight loss⁸.

Embolization of such material can lead to variable degrees of clinical manifestations, the time between procedure and symptoms ranges between 1h to 3 months¹⁰, clinical presentation include: "blue toes syndrome", normal peripheral pulses associated

with "levido reticularis" of the lower limbs which is reddish-violet reticular discoloration of the skin. It is caused by an interruption of blood flow in the dermal arteries, either due to spasm, inflammation, or vascular obstruction¹⁷; renal insufficiency in which the typical renal syndrome is a continuous decline in renal function occurring over weeks with concomitant worsening of hypertension due to increased renin-angiotensin activity with up to 50% of patients require dialysis¹⁸; non-occlusive mesenteric vascular ischemia manifests as an abdominal pain and hemorrhage due to mucosal ulceration, ischemia, infarction, and perforation by cholesterol emboli¹⁹, neurological deficits²⁰, even fever of unknown origin¹⁰. Rare manifestations of CCE include pancreatitis²¹, acalculous cholecystitis²², adrenal insufficiency, and pulmonary embolization²³. Cholesterol emboli also have been demonstrated in the coronary circulation causing myocardial infarctions²⁴.

Overall, a 60 to 80% mortality rate has been associated with this disease, with the cause of death most often being multifactorial²³. However, given that these data are derived from case reports, there is most likely a bias toward severe cases with many cases of CCE being subclinical. Nonetheless, two case series have suggested that when CCE is complicated by renal failure the mortality rate is up to 75%^{25,26}.

Laboratory abnormalities are common in CCE. In the review by Fine et al⁸, a majority of patients had an elevated erythrocyte sedimentation rate and up to one third had an erythrocyte sedimentation rate over 100 mm/hr. Azotemia is present in up to 80% of patients²⁷. In several series⁸⁻¹¹ eosinophilia has been reported to occur in approximately 75% of patients, although other series²³ suggest a prevalence of less than 25%. The variability in the reported prevalence may be due to the transient nature of the eosinophilia²². Fukumoto et al¹¹ found an interesting observation while searching for an independent predictor of CCE, multivariate regression analysis identified only the elevation of pre-procedural CRP levels (odds ratio 4.6, P = 0.01).

Histologically, the diagnosis of CCE is made by the presence of cholesterol crystals in the lumen of a blood vessel in a biopsy or autopsy specimen²³. Given the increasing awareness of CCE, premortem diagnosis of this condition using skin biopsy may increase in frequency²⁶. Diagnosis of non-occlusive

mesenteric vascular ischemia is based on findings of angiography²⁸.

Many forms of therapy have been attempted²⁹, including corticosteroids and antiplatelet agents, neither of which has been shown to have an effect³⁰. As initiation of anticoagulation therapy can precipitate cholesterol embolization, cessation of therapy has been tested as a means to minimize further embolization, with variable success³¹. pentoxifylline and cholesterol-lowering agents have been used with isolated reports of success³².

Patients requiring cardiac surgery are at high risk of developing CCE. With the triggering factors of left heart catheterization, aortic cannulation, cross-clamping, and anticoagulant therapy (before, during and after surgery). We may add in our case the intra-aortic balloon as a possible triggering factor as well. It is well documented that intraoperative manipulation of the aorta during cardiac surgery correlates with systemic embolization¹⁰ by studying embolic signals with transcranial Doppler during cardiopulmonary bypass for coronary bypass surgery, Barbut et al³³ showed that all patients displayed embolic signals. Most have been recorded during removal of aortic cross clamps and partial occlusion clamps.

The use of intraoperative echocardiography of the ascending aorta and aortic arch has been useful to assess the degree of atherosclerosis³⁴⁻³⁶. Surgical palpation as a method of assessing atherosclerotic plaque grossly underestimates the presence and severity of disease³⁷. Furthermore, the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists recommends intraoperative epi-aortic scanning as a more superior modality for patients with an increased risk for embolic stroke suggested by

clinical history or intraoperative TEE³⁸.

In case of severe aortic atherosclerosis it might be necessary to modify the standard cannulation and clamping techniques³⁹, to use filtration devices of the ascending aorta⁴⁰ or even perform off-pump surgery and use of arterial grafts^{39, 41}. Although some case reports refer to CCE after off-pump bypass⁴², this could be related to aortic manipulation by side clamp. Kapetanakis et al⁴³ studied 7,272 patients who underwent isolated CABG surgery through three levels of aortic manipulation: full aortic clamp application, tangential (side-biting) aortic clamp application and "aortic no-touch" technique, the incidence of stroke was lower by almost 50% in the "no-touch" group.

The authors believe that among Saudi population, patients going for cardiac surgery might be at a higher risk of this syndrome, considering the well established higher incidence of atherosclerosis, diabetes and hypercholesterolemia in Saudi Arabia^{44,45}, all are basic risk factors of cholesterol embolization.

This is a case of clinically proven cholesterol crystal embolization (CCE) that lacks histological confirmation. The high mortality of CCE may be the result of the diverse clinical presentation and the poor clinical recognition of this disorder. Clinicians, surgeons and pathologists should be aware of the risk of CCE after cardiac surgery. Moreover, Symptoms related to CCE must be sought before CABG: renal insufficiency after left heart catheterization associated with eosinophilia, blue toes syndrome and livido reticularis. These symptoms indicate the need for a skin or muscular biopsy. Adequate future strategies to prevent the disease are necessary, since no proven effective treatment of this dangerous complication is known.

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