Cholesterol Emboli Syndrome

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We present the case of a 55-year-old patient who developed cholesterol embolism 10 days after routine coronary angiography. The possible source of emboli was a large ulcerated atherosclerotic plaque of the thoracic aorta. The patient developed permanent, necrotic, painful skin lesions on his toes and end stage renal failure. Due to intractable angina he was considered for coronary bypass grafting but died suddenly.

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Cholesterol crystal embolization syndrome is a clinical entity that is recently being diagnosed more often. It is thought to be a complication of atherosclerosis and is found in 2-8% of necropsies.[1] It often follows invasive procedures involving the aorta and major arteries, such as angiography, angioplasty and cardiovascular surgery.[2-4]

Organs most frequently involved are the skin and the kidneys, but any other organ can be affected. Cutaneous manifestations vary from livedo reticularis and acrocyanosis (blue toe syndrome), which are seen most frequently, to nodules, ulcers, purpuric lesions and gangrene. Renal failure is documented in 50% of cases and gastrointestinal bleeding in 10%.[4] Less common features of the syndrome include central nervous system and coronary artery disease manifestations, ischemic pancreatitis and gastrointestinal ischemia, as well as the fatal multiple cholesterol emboli syndrome.[5] The pathophysiology of the syndrome includes the dislodgement of cholesterol crystals from ulcerated atheromatic plaques, usually lining the walls of the aorta, and residual embolization of periphery arterioles with a diameter of 100-200 μm.[2]

We describe the case of a 55-year-old patient who developed cholesterol embolism following routine coronary angiography.

Case presentation

A 55-year-old patient with a history of hypertension, dyslipidemia and smoking underwent routine coronary angiography following a positive treadmill exercise test. Angiography was uneventful and showed a severe right coronary artery (RCA) stenosis, moderate stenosis of the circumflex (CX) artery and complete occlusion of the left anterior descending artery (LAD). The LAD was a diffusely but severely stenosed vessel, which was only visualized in part. Ejection fraction was approximately 60%. Because of catheter tortuosity during the procedure, a descending aorta angiography was performed.

Next day the patient complained of muscular pain in his calves and feet. Clinical examination, involving artery pulsation, and blood tests were normal. The patient's condition was evaluated by a vascular surgeon and finally he was discharged on low molecular weight heparin. During the following days his symptoms became more severe and he developed cutaneous blue spots of various sizes on his torso and legs. This was the clinical picture when he presented at the emergency department of our hospital ten days after

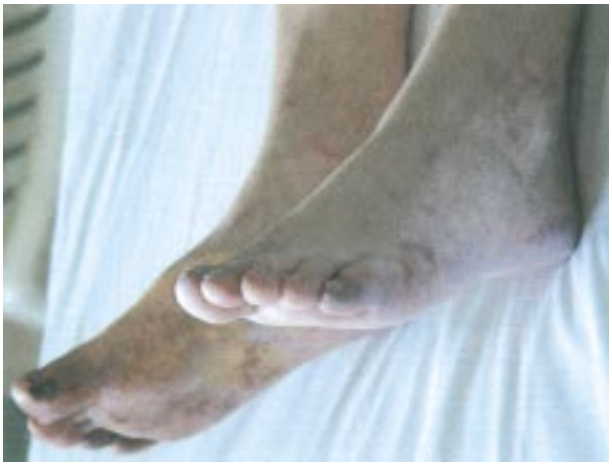


Figure 1. Typical livedo reticularis of both tibia and feet.

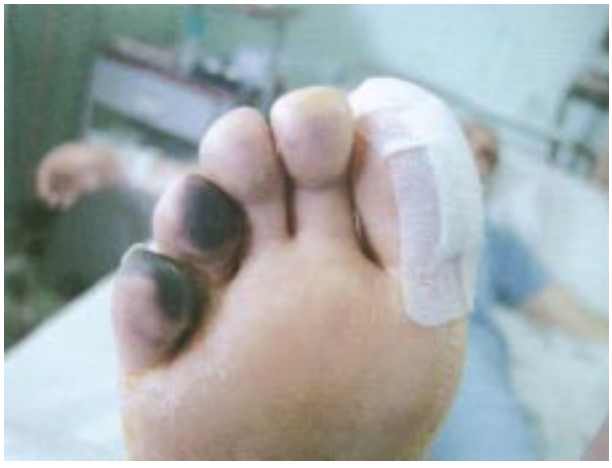


Figure 2. Blue toe syndrome involving the right 4th and 5th toes with additional ischemic lesions in the others. Biopsy was taken from the first toe.

coronary angiography and he was admitted with the diagnosis of "ischemic type cutaneous feet lesions".

Clinical examination revealed the following: BP=145/80 mmHg, pulse=75/min, RR=15/min, T=36.8˚C.

Skin: bilateral tibial livedo reticularis and blue toe syndrome involving all toes on both feet, presenting with painful cyanotic lesions and some necrotic lesions on his right 4th and 5th toes (Figures 1, 2).

Cardiovascular system: S1, S2 were normal; 2/6 apex systolic murmur. Artery pulsation was normal without any evident murmurs.

Respiratory system: normal findings.

Muscular system: Both calves were painful without any evidence of inflammation.

Gastrointestinal system: flatulence, reduced peristalsis and some diffuse abdominal tenderness.

Blood tests showed the following: Ht = 43.7 %, Hb = 14.8 g/dL, WBC = 15500 c/mm^3 (poly = 63%, lymph = 25%, eosinoph = 18%), PLT=347000c/mm^3

Erythrocyte Sedimentation Rate (ESR)=68 mm, CRP=7.92 mg/dL, PT=11/11, PTT=32/30, Fibrinogen=806 mg/dL, D-Dimers=3.29 μg/ml, FDP=4 μg/ml, Glucose=116 mg/dL, Urea=85 mg/dL, Creatinine=2.6 mg/dL, K^+=5.2 mEq/L, Na^+=138 mEq/L, CPK=377 IU/L (CK-MB=15 IU/L), AST=31 IU/L, ALT=25 IU/L, LDH=513 IU/L, Cholesterol=244 mg/dL, Triglycerides=133 mg/dL, HDL=31 mg/dL, LDL=182 mg/dL. Blood gases: pH=7.46, PO_2=87 mmHg, PCO_2=36 mmHg, SO_2= 98%. Urine analysis showed minor proteinuria.

History (previous coronary angiography), clinical examination (cutaneous lesions) and blood tests (renal failure, leucocytosis with eosinophilia), led to the diagnosis of cholesterol emboli syndrome. ACE inhibitors and heparin were discontinued and the initial treatment included nitrates, felodipine (10 mg od), atorvastatin (40 mg bid), buflomedil (600 mg od), pentoxyphylline (400 mg bid) and amoxycillin-clavulanic acid (i.v. 1.2 g tid). Immunologic blood tests carried out in order to exclude a non-mechanical cause of blue toe syndrome were negative.

To confirm the diagnosis (aorta ulceration-emboli source) the patient underwent transesophageal echocardiography, which revealed a large atherosclerotic ulcerated plaque with mobile atheromatic debris within the lumen of the descending aorta, immediately after the origin of the left subclavian

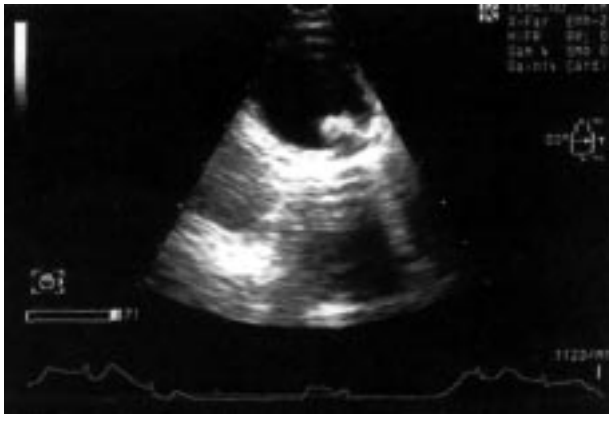
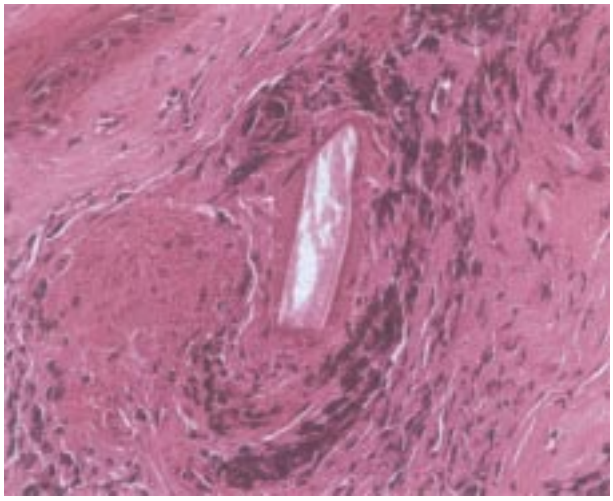


Figure 3. Large mobile atheroma within the descending aorta lumen (transesophageal echocardiography).



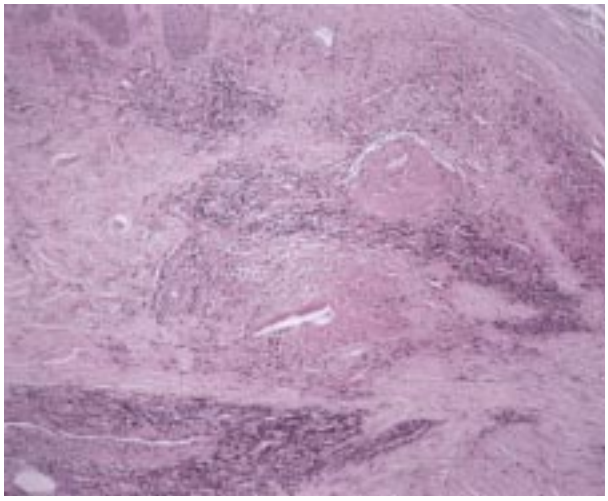


Figure 4, 5. Typical cholesterol crystal clefts and giant cell perforation within an arteriole lumen.

artery (Figure 3). In order to exclude similar embolic sources, we carried out an echo examination of the great abdominal vessels, which proved to be normal. Contrast computed tomography was not performed in view of the impaired renal function. The diagnosis was confirmed by histological examination of a skin lesion particle (Figures 4, 5).

On day 3 of admission, by which time symptoms had become more severe with deterioration of the cutaneous lesions and severe paroxysmal episodes of pain, we began intravenous infusions of a prostacyclin analogue (Ilomedin) for about 6 hours daily, in a gradually increasing dosage until the target dose of 30 μg/kg/min. The skin lesions showed a modest improvement, but 5 days later demonstrated necrotic features in all 5 left toes. This finding, in relation to the patient's epigastric discomfort and abdominal pain, the high blood amylase value (88 mg/dL) and the permanent eosinophilia, were indicative of a recurrence of embolization.

On day 12, echo examination established the normal size of both kidneys, while an isotope renogram confirmed diffuse arterial occlusion and a decline in renal function (Figure 6). This decline was gradual and on day 26, when the patient started dialysis, the urea value had reached 140 mg/dL and creatinine 8.66 mg/dL (Figure 7).

The patient was discharged after 39 days of hospitalization and was on a dialysis schedule three times weekly. His symptoms were controlled with subcutaneous transdermal fentanyl infusion but the

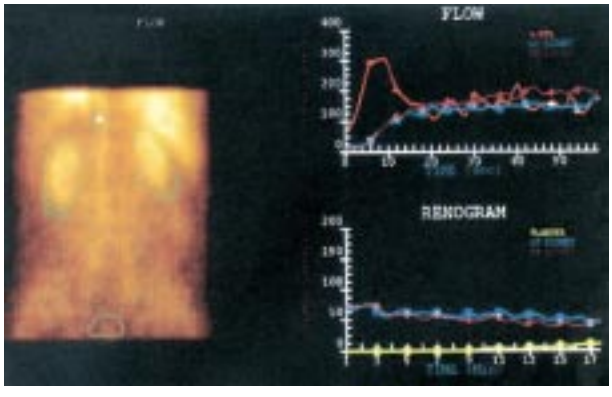


Figure 6. ^{99m}Tc-DTPA renogram. Typical flat perfusion (above) and renal function curves having identical perfusion and excretion phase (below).

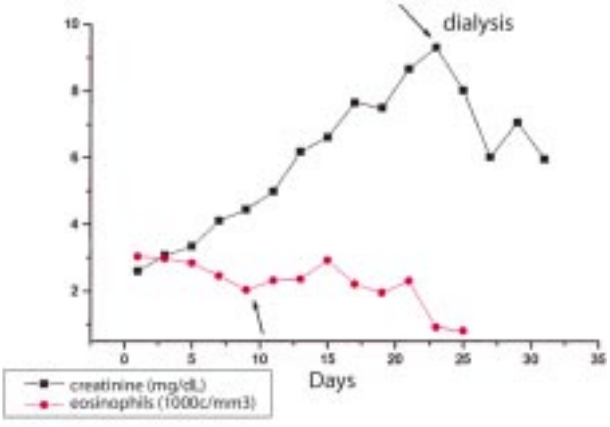


Figure 7. Variations in creatinine levels and eosinophil count during patient hospitalization. The first arrow indicates the evolution of recurrent embolism with subsequent eosinophil count augmentation. The second arrow indicates the 26th day of admission when the patient began dialysis and creatinine levels started to fall.

skin lesions advanced to necrotic, in spite of Ilomedin infusion cycles. One month later he was admitted for unstable angina and developed inferior myocardial infarction with an uneventful postinfarction course. He was finally discharged, but was admitted again 40 days later suffering from unstable angina (long lasting ischemic episodes with severe ST segment depression in all ECG leads unresponsive to conventional therapy). The patient was considered for off pump coronary artery bypass grafting (CABG) with the use of arterial grafts but he suddenly developed cardiogenic shock with electromechanical dissociation and died.

Discussion

Cholesterol emboli syndrome is due to dislodgement of atheromatic debris and emboli formation from ruptured atherosclerotic plaques lining the walls of the aorta and the major arteries. It may occur spontaneously but often follows cardiovascular surgery or coronary angiography and angioplasty (0.08%).[6] Due to the crystal morphology, occlusion of the vessels is not always complete, giving rise to ischemic atrophy rather than necrosis. Subsequently, a "foreign body" type response occurs, with intima hypertrophy, giant cell sequestration and further luminal stenosis. This mechanism is responsible for the characteristic gradual decline of renal function, which develops over a period of 3 to 8 weeks. Risk factors are old age, peripheral vascular disease, severe atherosclerosis of the ascending aorta and repeated invasive procedures. The syndrome may appear following the use of coumadine products, heparine or thrombolytics, where the non-effective coating of a ruptured atheromatic plaque by thrombus might be the possible induction mechanism. The use of these agents, high creatinine levels, low platelet count and the large size of diagnostic catheters are thought to represent minor risk factors for the evolution of this syndrome.[1,6]

Cholesterol embolization is not a common clinical entity: it is rarely diagnosed in life but can have serious consequences. It is characterized by the classic triad of ischemic skin lesions, acute renal failure and eosinophilia, findings which were evident in our patient. Any organ may be affected (in our case there was evidence of mild pancreatitis) but sometimes it may show atypical features such as fever, muscular pain or manifestations of systemic vasculitis.[7] The time interval between intervention and disease onset is typically 1 to 4 weeks, but occasionally may extend to several months. This specific "time window" and the subsequent and gradual deterioration of renal function may help to distinguish cholesterol embolism from contrast nephropathy.

Part of the clinical picture may be the appearance of the so-called blue toe syndrome, which is a completely different entity of varying etiology and is characterized by cyanotic toe skin lesions with no renal failure and where the treatment is purely etiologic (includes the use of coumadine or low molecular weight heparin, which are contraindicated in cholesterol embolism).[8]

Knowledge and awareness of the syndrome, as well as a detailed history, are of great importance for correct diagnosis. Blood tests reveal renal dysfunction and the striking eosinophilia, which is encountered in 70 to 80% of cases, is usually an early finding.[9] Elevated erythrocyte sedimentation rate and hypocomplementemia are common. Urine analysis usually shows modest proteinuria with or without hematuria, while high blood amylase levels, melena or anemia may be encountered in the multi-organ type of the syndrome.

The diagnosis can be confirmed by biopsy of the skin, muscle or kidney, which demonstrates the characteristic appearance of cholesterol crystal clefts, with giant cell perforation into the arteriole lumen (Figures 4,5). Occasionally, the crystals can be seen as emboli in the retinal microcirculation in patients with ischemic stroke.

Transesophageal echocardiography seems to be an invaluable diagnostic tool in the evaluation of the syndrome, demonstrating in detail the anatomy of heart and aorta, as well as mobile atheromata.[10] Angiography should be avoided in view of the possible recurrence of embolism. Finally, two dimensional echo of the great vessels, computed tomography and magnetic resonance imaging may appear helpful.

Mortality varies in the literature and is estimated to be between 64 and 81%.[1] Death is usually of cardiovascular origin and very often these patients develop end stage renal failure dependent on dialysis. The worst prognosis is encountered in the multiple cholesterol emboli syndrome with mortality reaching 100%.[5]

Treatment options are limited. In recent years, a conservative approach with the avoidance of any further vascular intervention due to the potent embolism recurrence has been considered the best option.[11] The discontinuation of coumadine products and

antiplatelet agents, which may limit or inhibit the atherosclerotic plaque coating by thrombus is of great importance. Statins might stabilize plaques,[12] while steroid treatment remains controversial.[11] Our patient was on a high dose of atorvastatin (80 mg/d) but the dosage was modified to 40 mg/d because of gastrointestinal side effects.

There are recent reports of beneficial effects from a prostacyclin analogue (Ilomedin) on renal function and cutaneous lesions,[13] but this did not occur in our patient, who first experienced a modest improvement followed by recurrent embolism and clinical deterioration. As far as treatment options for painful skin lesions are concerned, it seems that intermittent epidural analgesia promotes the best results.[9] Spinal cord stimulation has been recognized as a quite effective method for pain control and its established ability to improve peripheral microcirculation may allow an efficient resolution of necrotic lesions.[14] Our patient refused to undergo any of the two proposed supportive treatments.

It must be emphasized that patients with a history of blue toe syndrome or cholesterol embolism, and those manifesting the risk factors that have been discussed, should be managed with heightened caution when they undergo cardiovascular procedures. Additionally, when surgery cannot be avoided, transesophageal echocardiography, delineating the aortic anatomy in great detail, and off-pump CABG with the use of arterial grafts are strongly recommended.[15] Our patient was considered for such a procedure, but died suddenly.

In conclusion, the incidence of cholesterol emboli syndrome seems to be increasing following the widespread growth in the practice of invasive cardiology. Accordingly, patients prone to developing this devastating clinical syndrome should be managed with extreme attention, in order to make the diagnosis promptly and to begin supportive treatment as soon as possible.

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