Cholesterol emboli

Synonyms: cholesterol embolism syndrome (CES), cholesterol crystal embolisation (CCE), atheroembolism

What are cholesterol emboli?[1]

Cholesterol crystals and associated components of atheromatous arterial plaques may embolise spontaneously, as a result of vascular instrumentation, or following other destabilisation of the organised thrombotic surface of a plaque.

Cholesterol-embolisation syndrome (CES) is a systemic disease caused by showering of atherosclerotic plaque materials, such as cholesterol crystals, from the aorta and its major branches to the distal circulation, leading to ischaemic and inflammatory damage to multiple organs.

See also separate articles Limb Embolism and Ischaemia and Bowel Ischaemia.

Pathogenesis

The following six factors are required for the development of cholesterol embolisation syndrome:[2]

- Plaque in a proximal, large-calibre artery (such as the internal carotid artery, the iliac arteries, or the aorta).
- Plaque rupture - which may be spontaneous, traumatic, or iatrogenic.
- Embolisation of plaque debris (containing cholesterol crystals, platelets, fibrin, and calcified detritus).
- Lodging of the emboli in small-to-medium arteries, leading to mechanical occlusion.

- Foreign-body inflammatory response to cholesterol emboli.
- End-organ damage due to mechanical plugging and inflammation.

The lungs are spared from direct damage from cholesterol emboli, but may suffer damage from inflammation.

How common is cholesterol emboli? (Epidemiology)

CES is probably underdiagnosed. It is an uncommon consequence of a very common disease (atherosclerosis). There is an appreciable background prevalence in the general population, particularly in older, male patients.

The incidence of clinically evident CES has been reported to be 0.09%–2.9%. In autopsy series, CES was found at a frequency of 0.31%–2.4%. However CES frequency was significantly higher (12%–77%) in autopsy studies performed on selected populations, such as older adults who had died after aortic surgery or aortography.[1]

Risk factors[3]

- Vascular intervention, especially with femoral access route.[4]
- Male gender.
- Age over 50 years.
- Known atherosclerosis.
- History of hypertension.
- Smoking.
- Elevation of C-reactive protein (CRP) before arterial instrumentation.
- Anticoagulation.
- Co-existence of mitral valve annular calcification.

It can uncommonly affect those who develop accelerated atheromatous disease due to dyslipidaemia or other causes of enhanced vascular risk.

Cholesterol emboli symptoms (presentation)

The most common embolic source is the aorta, so it tends to cause disruption of blood supply to the visceral organs and lower extremities. The syndrome should be considered as a cause of deteriorating renal function, worsening hypertension, distal ischaemia or sudden-onset multisystem dysfunction after an invasive arterial procedure.

The syndrome can manifest in a myriad of presentations, making diagnosis a challenge. It may directly affect all tissues of the body with the exception of the lungs. However, systemic inflammatory mediators released by cholesterol emboli may affect pulmonary tissues.

Symptoms and signs

Cholesterol embolisation is characterised by a nonspecific acute inflammatory response leading to constitutional symptoms including:[2]

- Fever.
- Cachexia.
- Nonspecific malaise.
- Myalgia.
- Acute respiratory distress syndrome (ARDS) due to circulating inflammatory mediators.
- Hypercatabolic state.

Cholesterol emboli originating in the descending thoracic and abdominal aorta may lead to renal failure, gut ischaemia, and emboli to the skeletal muscles and the skin.

Cholesterol emboli originating in the ascending aorta may in addition cause neurological damage that is typically diffuse and due to small infarcts.

Dermatological manifestations (most commonly livedo reticularis and blue toe syndrome) are usually confined to the lower extremities but may extend to the abdomen and the chest.

Differential diagnosis

The differential diagnosis of cholesterol-embolisation syndrome includes arterial thromboembolism associated with:[1]

- Contrast-induced acute kidney injury.
- Ischemic acute tubular necrosis.
- Drug-induced interstitial nephritis.
- Endocarditis.
- Aortic dissection.
- Left atrial myxoma.
- Lymphoma.
- Tuberculosis.
- Secondary syphilis.
- Pheochromocytoma.
- Raynaud's phenomenon.
- Vasculitis (polyarteritis nodosa, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, thromboangiitis obliterans).
- Cryoglobulinaemia.
- Antiphospholipid syndrome.
- Polycythemia vera.
- Thrombotic thrombocytopenic purpura.

Investigations

The gold standard of CES diagnosis is tissue biopsy, which may be obtained from skin, muscle, kidney, bone marrow, and gastric and colonic mucosa.[1] Other investigations may include:

- FBC reveals leukocytosis in some cases but is nonspecific.
- Eosinophilia (found in early days in 80% patients).[3]

- U&Es nearly always show varying degrees of elevated urea and creatinine.
- Creatine kinase, cardiac enzymes, LFTs and amylase may be elevated.
- Urine microscopy shows hyaline casts and eosinophils (strongly suggestive of the diagnosis).
- Urinalysis may show microscopic haematuria and proteinuria.
- Elevated CRP before arterial instrumentation is a useful predictive factor with an odds ratio of 4.6.[3]
- Indicators of an excess of inflammatory mediators may be suggested by elevation of ESR, CRP, rheumatoid factor and antinuclear antibodies. Low complement levels may be found.
- Angiography may be considered to look for other causes of vascular compromise and is also a cause of the condition.
- Transoesophageal echocardiography, helical CT angiography and MRI angiography may detect unstable atheromatous disease in the aorta and suggest the diagnosis in conjunction with typical features.

Cholesterol emboli treatment and management[5]

Treatment is mainly supportive and aimed at seeing the patient through the effects of multi-organ dysfunction or acute respiratory distress syndrome (ARDS). Currently, no treatment is available for direct removal of cholesterol crystals that cause mechanical occlusion and no treatment is available for irreversible damage.

Therefore, the goal of treatment is to minimise the secondary inflammatory response that triggers the foreign body reaction against crystals and to prevent irreversible damage to target organs. Treatment for inflammatory reactions should be initiated as soon as possible.

Corticosteroids have produced mixed results but reports have shown effective improvement. The optimal dose and duration of corticosteroid treatment have not yet been determined. Combination therapy with other anti-inflammatory agents may increase effectiveness of treatment, but may further exacerbate the risk of infection due to immunodeficiency.

Prostaglandin E1 is a drug that can be used safely and is also effective in treating cholesterol embolism. Prostaglandin E1 has vasodilating activity, resulting in the inhibition of platelet aggregation and modulation of cell proliferation. Combination therapy with corticosteroids and alprostadil may be more effective than monotherapy.

Therefore, the management of cholesterol-embolisation syndrome may include:[1]

- Secondary prevention of cardiovascular disease.
- Anti-inflammatory treatments, eg, corticosteroids.
- Other medical treatments may include iloprost, dipyridamole, pentoxifylline, and withdrawal of anticoagulants if not otherwise indicated.
- Interventional and surgical treatments may include: stent and endograft implantation, endarterectomy and bypass surgery.

Complications

- Worsening renal impairment.
- Accelerated or malignant hypertension.
- Ischaemia and dysfunction of organs and viscera/tissues of peripheral limbs.
- Dermatological lesions.
- Acute respiratory distress syndrome (ARDS).
- Catabolism and cachexia.
- MI or impairment.
- Neurological dysfunction.
- Adrenal failure.
- Multi-organ failure and death.

Prognosis

The prognosis is usually poor with high mortality, probably due to advanced atherosclerosis and related comorbid cardiovascular diseases. Renal involvement in CES may have important adverse prognostic implications. [1]

Prevention of cholesterol emboli

Because cholesterol embolisation syndrome is a manifestation of atherosclerosis, modification of traditional risk factors such as smoking, hypertension and serum cholesterol should be advised strongly. There is some evidence that statin therapy decreases the risk of cholesterol embolisation syndrome. [2]

- Careful balancing of risks and benefits in patients about to undergo arterial instrumentation who are known to have, or are at high risk of, atheromatous vascular disease.
- Checking of pre-procedure CRP may be useful as a predictive indicator, and may influence opinion of the risk/benefit balance.
- The use of brachial or radial artery approaches was thought to reduce the risk of the syndrome, but analyses have failed to support this assumption, leading to the conclusion that the aorta is the major embolic source. [3]
- Surgical techniques, involving careful siting of aortic clamps and gentle manipulation of the aorta during cardiac or aortic surgery, may reduce the incidence of the disease in this high-risk cohort.

Further reading

- Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk; European Society of Cardiology/European Atherosclerosis Society (2019)
- CVD risk assessment and management; NICE CKS, May 2023 (UK access only)
- Shah N, Nagalli S; Cholesterol Emboli. StatPearls, July 2022.

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