CORONARY HEART DISEASE (JA FARMER, SECTION EDITOR)

The Cholesterol Emboli Syndrome in Atherosclerosis

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Abstract Cholesterol emboli syndrome is a relatively rare, but potentially devastating, manifestation of atherosclerotic disease. Cholesterol emboli syndrome is characterized by waves of arterio-arterial embolization of cholesterol crystals and atheroma debris from atherosclerotic plaques in the aorta or its large branches to small or medium caliber arteries (100–200 μm in diameter) that frequently occur after invasive arterial procedures. End-organ damage is due to mechanical occlusion and inflammatory response in the destination arteries. Clinical manifestations may include renal failure, blue toe syndrome, global neurologic deficits and a variety of gastrointestinal, ocular and constitutional signs and symptoms. There is no specific therapy for cholesterol emboli syndrome. Supportive measures include modifications of risk factors, use of statins and antiplatelet agents, avoidance of anticoagulation and thrombolytic agents, and utilization of surgical and endovascular techniques to exclude sources of cholesterol emboli.

Keywords Atherosclerosis · Atheroma · Cholesterol emboli · Plaque

Introduction

The cholesterol emboli syndrome (CES) is a rare arterio-arterial embolization syndrome which occurs when cholesterol crystals located in an atherosclerotic plaque in a large caliber artery (typically the aorta) embolize to small or medium caliber arteries, which then results in end-organ damage secondary to either mechanical obstruction and/or inflammatory response [1•]. This syndrome has also been referred as atheroembolism, atheromatous embolization syndrome, cholesterol crystal embolization and cholesterol embolization syndrome [2].

It is important to emphasize that CES is a separate entity from a more common phenomenon of another arterio-arterial embolization syndrome, namely arterio-arterial thromboembolism, in which a thrombus overlying an atheromatous plaque breaks loose and travels distally to occlude large-caliber downstream arteries [3]. In arterio-arterial thromboembolism, there is typically a sudden release of thrombi, resulting in acute ischemia of a target organ. In contrast, CES is characterized by multiple, small cholesterol crystal emboli that are released over a period of time [4•].

CES is but a manifestation of generalized atherosclerosis [5••]. A wide variety of clinical presentations of CES have been reported. Clinical manifestations are primarily dependent on the location of the atheromatous plaque that serves as the source of cholesterol emboli, as well as the location of the affected distal arterial bed. Cholesterol crystal emboli that arise from the descending thoracic aorta may lead to renal failure, mesenteric ischemia and emboli to the skeletal muscles and skin. Emboli arising from the ascending aorta may also result in neurological compromise, frequently due to multiple infarcts. In addition to specific signs of end-organ damage, CES is often characterized by systemic signs and symptoms due to nonspecific acute inflammatory response. Systemic manifestations may include fever, malaise, hypereosinophilia and elevation in inflammatory serum markers such as elevated erythrocyte sedimentation rate and C-reactive protein [6].

History

Probably the first case of apparent CES was reported in 1844 by a group of Danish physicians after performing the autopsy of Bertel Thorvaldsen, a famous Danish/Icelandic

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sculptor [7]. In 1862, this report was translated into German by Peter Ludvig Panum, another Danish physician, and disseminated into the broader medical literature [8].

The first autopsy series of CES was published in 1945 from New York Hospital, and contains classic descriptions of the systemic and multiorgan nature of this syndrome [9]. To this day, the definitive diagnosis of CES still relies on biopsy of affected organs; biopsy techniques for visualizing of cholesterol crystals lodged in destination arteries using polarized light were first reported in the 1950s [10].

In 1961, Robert Hollenhorst, an ophthalmologist from the Mayo Clinic, described pathognomonic retinal plaques consisting of refractive yellow cholesterol emboli at branching points of retinal arteries. This discovery allowed for the first time to diagnose CES noninvasively [11]. In 1976, the term blue-toe syndrome was first coined; the term that is now partly synonymous with CES [12]. In 1990, for the first time, an association between clinical syndromes of atheroembolism and aortic plaques seen on transesophageal echocardiography was reported from New York University [13].

Pathophysiology

The pathophysiology of CES involves six key elements: the presence of an atherosclerotic plaque in the proximal large-caliber artery, plaque rupture, embolization of plaque content, lodging of cholesterol crystal emboli in distal small-caliber arteries, foreign body inflammatory response to cholesterol emboli and end-organ damage.

Atherosclerotic Plaque in a Proximal Artery

Development of atherosclerotic plaques is a life-long process (Table 1). Plaques reside within the arterial intima. In early stages, which typically developed in childhood and early adulthood, plaque lesions consist of intracellular and extracellular lipid deposits and are clinically silent. In more advanced stages, which typically develop in middle-aged and elderly individuals, the plaque histology becomes more complex and undergoes progressive changes from atheromas to fibroatheromas to complex plaques with hemorrhage, surface ulcerations and formation of overlying thrombi [14]. These advanced atherosclerotic plaques are the usual source of cholesterol crystal emboli in CES. During the progression of atherosclerosis calcifications may occur within plaques.

Atheromas are composed of a necrotic core; when overlaid by a fibrous cap they are referred to as fibroatheromas. Necrotic core consists of foam cells, cell debris and lipids. Low-density lipoprotein is the ultimate source of cholesterol emboli. Cholesterol exists in crystalline and soluble forms. Crystalline cholesterol represents >40 % of cholesterol within a plaque [15]. The cap is composed of endothelial and smooth muscle cells, as well as connective tissue.

Cap disruption precedes embolization of plaque contents. Rupture of this fibrous cap may be a result of forces from within the plaque (such as inflammation and hemorrhage), or from the luminal side (such as shearing forces or mechanical disruption). The risk of embolism is directly correlated with the overall degree of atherosclerosis. Typically, the amount of plaque increases from the proximal to distal segments of the aorta. Thus, the abdominal aorta and iliofemoral vessels are most frequent sources of emboli in CES [16].

Ante mortem visualization, characterization and quantification of plaque in the aorta can be achieved by transesophageal echocardiography (TEE), computerized tomography (CT) or magnetic resonance imaging (MRI) [17••, 18]. Simple plaques measure <4 mm in thickness. Complex plaques measure ≥4 mm and often have irregular, ulcerated borders, and may have mobile components that represent thrombi (Fig. 1).

Plaque thickness ≥4 mm in the ascending aorta or aortic arch as visualized by TEE has been strongly correlated with cerebral embolization events [13, 19, 20]. Complex atheroma visualized by TEE have been documented in patients with biopsy-proven cholesterol emboli to the kidneys and skin [21, 22]. CT and MRI have become increasingly popular noninvasive imaging techniques to characterize atherosclerotic plaque [23, 24]. Limitations of TEE (such as inability to

Table 1 Classification of atherosclerotic plaques

| Onset	Stage	Lesion Name	Description	Clinical Manifestations
Early Lesions (Childhood and Early Adulthood)	I	Initial Lesion	Small amounts of intracellular lipid deposits	Typically silent
	II	Fatty Streak	Larger amounts of intracellular lipid deposits	
	III	Intermediate Lesion	Small extracellular lipid deposits	
Late Lesions (Middle Age and Elderly	IV	Atheroma	Extracellular lipid core	Silent or clinically overt
	V	Fibroatheroma	Lipid core with fibrotic changes	
	VI	Complex Plaque	Surface defects such as ulcerations, hemorrhage and thrombus.	
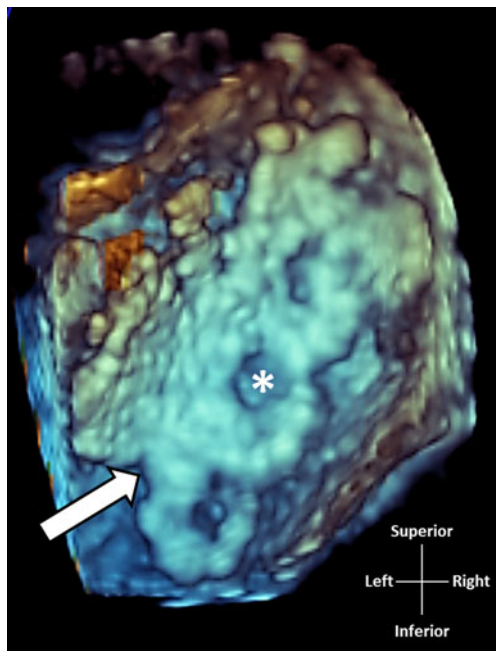
Fig. 1 Atherosclerotic plaque on 3D transesophageal echocardiography. Advanced (stage VI) atherosclerotic plaque (arrow) at the junction of the distal aortic arch and the proximal descending thoracic aorta, visualized by 3-dimensional TEE and presented as seen from the patient's back. There are multiple plaque ulcerations, one of which is labeled with an asterisk

visualize the brachiocephalic artery or the abdominal aorta) can be overcome by CT or MRI imaging. Aortography lacks sufficient sensitivity for detection of aortic plaques [25].

Plaque Rupture

Atherosclerotic plaque rupture may be spontaneous, traumatic and/or possible related to thrombolytic and anticoagulation therapy.

Spontaneous Atheroembolism Spontaneous plaque rupture in the aorta shares the same overall pathophysiology of spontaneous plaque rupture in other arterial beds. The instability of plaques is triggered by the complex interaction of adhesion molecules, monocytes, macrophages, endothelial cells, cytokines, transmitters and proteolytic enzymes [26]. Prior to the widespread use of arterial cannulation for cardiovascular imaging and intervention (which are known risk factors for traumatic plaque rupture), the incidence of spontaneous atheroembolism, based on autopsy studies was reported to range from <1 %to 3.4 % [9, 27, 28].

Traumatic Plaque Rupture Traumatic plaque rupture may be related to blunt trauma or may result from iatrogenic manipulation of arteries, such as during catheterization or cardiovascular surgery. Although plaque debris has been

isolated from>50 % of guiding catheters in one series, CES is a relatively rare complication of cardiac catheterization [29]. The incidence of clinically apparent atheroembolism has been reported to occur in less than 2 % of all cardiac catheterizations [30, 31]. There is no significant difference between the risk of this complication when femoral access is compared to radial access, which suggests that the ascending aorta is the main source of embolus [32].

The risk of CES following cardiac surgery is strongly correlated with the degree of atherosclerosis in the ascending aorta. The brain is the most commonly reported site of emboli, although multiple peripheral organs may also be involved. CES has been more frequently reported in patients undergoing coronary revascularization when compared to those undergoing valvular procedures [33]. Off-pump cardiovascular surgeries may lead to less microembolization events compared to surgeries using traditional cardiopulmonary bypass techniques [34]. Cholesterol emboli has been observed following traditional carotid endarterectomy, as well as carotid stenting [35, 36].

Thrombolytic and Anticoagulant Therapy Several cases of cholesterol emboli after administration of thrombolytic therapy for acute coronary syndrome and deep vein thrombosis have been reported. Although a small prospective study failed to demonstrate a relationship [37], controversy still exists regarding the link between thrombolytic therapy and cholesterol embolization [38]. There is also controversy as to whether anticoagulation is an independent risk factor for CES. There are no randomized trials that specifically address the issue of anticoagulation and CES. Thus, a causal relationship between anticoagulation therapy and CES can neither be proven nor refuted with certainty.

Embolization Of Plaque Debris

CES is characterized by showers of multiple microemboli consisting of cholesterol crystals and plaque debris to various end-organ vascular beds, often over a period of time. This is in contrast to arterio-arterial thromboembolism, where relatively large pieces of thrombi from atherosclerotic plaques embolize distally in an abrupt manner. CES becomes clinically evident once end-organ damage is apparent.

Lodging Of Emboli In Small To Medium Arteries

Cholesterol emboli lodge in small arteries and arterioles whose diameter is typically in the range of 100 to 200 μm. In routine biopsy specimens, cholesterol crystals are not visualized per se as they are washed away during processing. Instead, typical ovoid or crescentic clefts within the lumen of affected vessels are seen, and they represent spaces

from which cholesterol crystals have been washed away [39]. Cholesterol crystals can be visualized directly in biopsy specimens preserved with liquid nitrogen using polarized microscopy. In such specimens, cholesterol crystals demonstrate birefringence (double refraction of polarized light) [10].

Inflammatory Response To Cholesterol Emboli

Asides from directly obstructing blood flow, cholesterol emboli also trigger an inflammatory response. This response consists of acute inflammation, foreign body reaction, intravascular thrombi formation and endothelial proliferation leading to fibrosis. The walls of the small arteries and arterioles become infiltrated by polymorphonuclear cells and eosinophils. Mononuclear cells later appear and become giant cells. These giant cells phagocytize cholesterol crystals. This is followed by intraluminal thrombus formation, endothelial proliferation and intimal fibrosis. This results in partial or complete occlusion of the lumen, which may lead to tissue ischemia [40].

End-Organ Damage

End-organ damage is a result of both mechanical obstruction and the inflammatory response. Any organ can be affected by cholesterol emboli syndrome. However, the brain, kidneys, gastrointestinal tract, skin and skeletal muscles of the lower extremities are the most frequently affected. Organ specific manifestations of CES are described below.

Central Nervous System

Cholesterol emboli showering from the ascending aorta, aortic arch, carotid or vertebral arteries lead primarily to diffuse brain injury. CES is typically characterized by global symptoms such as confusion and memory loss. This is in contrast to arterio-arterial thromboembolism, which typically leads to an abrupt onset of focal neurological deficits [41]. Transcranial Doppler (TCD) may be used to detect cerebral microemboli, which may include cholesterol crystals, fat, air or calcium. Unfortunately, TCD is unable to distinguish cholesterol emboli from other microemboli [42]. CES is typically associated with small ischemic lesions and border zone infarcts on brain imaging [43].

Kidney

When cholesterol crystals embolize to the kidneys, CES is also referred to as atheroembolic renal disease. In one series of patients of more than 60 years of age undergoing renal biopsy for diagnosis of acute renal insufficiency, cholesterol embolization was identified in 6.9 % of them. Many of these patients did not carry the clinical diagnosis of CES prior to the pathological diagnosis, suggesting that many cholesterol embolization episodes are clinically silent.

CES may also lead to subacute and chronic renal insufficiency. Renal involvement was seen in 50 % of pathological proven cases of CES in one series. Clinical manifestations include elevation of serum creatinine, as well as proteinuria [44]. Renal ischemia may also result in uncontrolled hypertension [45]. The degree of renal impairment after CES may vary from spontaneous resolution to end-stage renal disease requiring dialysis. Survival in patient with renal manifestations of CES is markedly reduced, and has been reported to be worse than in patients after acute myocardial infarction or in the general population of dialysis patients [46].

Gastrointestinal System

Bowel ischemia is the primary presenting symptom of cholesterol emboli affecting the gastrointestinal tract. This often results in chronic gastrointestinal blood loss from mucosal ulcerations in the setting of mucosal infarcts [47]. In advanced cases, there may be pseudopolyp formation, ischemic colitis or viscus perforation [48]. Rarely, cholesterol embolization syndrome may also result in necrotizing cholecystitis [49] or acute pancreatitis [50].

Skin

The term 'blue toe syndrome' has been used to describe some cutaneous manifestations of CES [12]. The frequency of skin involvement in cholesterol emboli syndrome has been reported in between 35 and 96 % of cases. Patients with renal manifestations have the highest incidence of skin involvement [51]. Cutaneous manifestations include livedo reticularis, gangrene, cyanosis, ulceration, nodules and purpura. The skin of the lower extremities is most often affected. However, the trunk and upper extremities may also be involved [52]. The frequent development of purple or blue discoloration of the lower extremity digits has lead to the creation of the term 'blue toe syndrome', which became partly synonymous with CES. Purple or blue discoloration is a reflection of microvascular ischemia and is not specific to CES per se.

Diagnosis of Cholesterol Emboli Syndrome

Usually, the diagnosis of CES is established clinically based on signs and symptoms that are specific to affected vascular

beds and often in patients with recent history of imaging or surgical procedures involving the aorta or its large branches. A typical patient is a middle aged or elderly male with risk factors for atherosclerosis, such as systemic hypertension, diabetes mellitus, hypercholesterolemia and a history of tobacco use [53].

Signs and symptoms specific to individual organs affected by CES were described above. The onset of signs and symptoms in CES is typically insidious as opposed to abrupt onset in arterio-arterial thromboembolism. As a consequence, there is typically no new loss of peripheral arterial pulses in CES, as compared to new pulse deficits frequently seen in arterio-arterial thromboembolism [54].

The presence of constitutional findings supports the diagnosis of CES. Constitutional signs and symptoms may include fever, weight loss, anorexia, fatigue and myalgias. Laboratory studies are often notable for elevated inflammatory markers (such as white blood cell count, erythrocyte sedimentation rate, fibrinogen and C-reactive protein) and/or decreased complement levels [30]. Anemia or thrombocytopenia may also be present. With renal involvement, elevated serum creatinine, hypereosinophilia, eosinophiluria and proteinuria have been frequently reported in this syndrome [55].

It is important to emphasize that, since in many instances signs and symptoms of cholesterol emboli syndrome are very non-specific, a high degree of clinical suspicion is essential in order to make this diagnosis. Hollenhorst plaques at the branching points of retinal arteries may be seen on ophthalmoscopy in patients in whom CES is caused by cholesterol crystal embolization from the proximal thoracic aorta, and carotid and vertebral arteries [11]. Visualization of advanced atherosclerotic plaques in the aorta or its major branches by ultrasound, CT or MRI techniques also supports the diagnosis of CES (Fig. 1).

Pathologic confirmation from a biopsy specimen is the only definite test for the diagnosis of CES [56]. Technically, a biopsy from any affected organ system can be used. However, the preferred sites are either the skin or the skeletal muscle, as they are less invasive than renal and gastrointestinal biopsies. However, tissues affected by CES are at risk for poor healing as the biopsied lesions are by definition in areas of compromised blood flow.

Treatment of Cholesterol Emboli Syndrome

There is no specific therapy for CES. Supportive therapy is aimed at alleviating end-organ damage and preventing further episodes of cholesterol emboli. Aggressive modification of atherosclerosis risk factors, including tobacco use, diabetes mellitus, hypertension, and serum cholesterol levels should be undertaken.

Based on nonrandomized trials, statin therapy has been shown to decrease the risk for CES [57]. There is no direct evidence for routine use of antiplatelet agents for the prevention of CES. However, their use seems reasonable, as they have been proven beneficial in patients with other manifestations of atherosclerosis, such as prevention of myocardial infarction [5]. Angiotensin converting enzyme inhibitors and angitensin receptor blockers may also be considered [58].

As previously noted, the relationship between CES and thrombolytic and anticoagulation therapy remains controversial. In principle, we do not recommend routine use of anticoagulation therapy in patients who are diagnosed with CES. The use of heparin, warfarin or thrombolytic agents has been associated with the development of CES, although a causal relationship has never been proven. However, if patients have a separate indication for anticoagulation, such as mechanical prosthetic valve, atrial fibrillation or deep vein thrombosis, anticoagulation therapy should be continued.

Surgical or endovascular treatment may be considered when a clear source of cholesterol emboli can be identified, the source is surgically or endovascularly accessible, and the patient is an appropriate surgical candidate. In such patients, surgical or endovascular treatment is aimed at removing or excluding the source of cholesterol emboli [59].

Conclusion

Cholesterol emboli syndrome is a form of arterio-arterial embolism seen in patients with advanced atherosclerosis and is characterized by high morbidity and mortality. The pathophysiology cascade of cholesterol emboli syndrome starts with a ruptured plaque in the aorta or a large proximal artery. The contents of the plaque (which include cholesterol crystals and atheroma debris) are released into the vessel lumen and travel distally as atheroemboli to small and medium-sized arteries. The ensuing ischemic end-organ damage occurs through a combination of mechanical obstruction and triggered inflammation in the target arteries.

Since there is no single clinical, imaging or laboratory finding that is unique to cholesterol emboli syndrome, a high degree of clinical suspicion is necessary for establishing the diagnosis. Ante mortem, the diagnosis of the cholesterol emboli syndrome can be confirmed by demonstrating either clefts or birefringent cholesterol crystals in end-organ biopsy specimens, typically obtained from skin or skeletal muscle. To this day, there is unfortunately no specific treatment for cholesterol emboli syndrome. Medical and surgical therapies are directed toward general management of atherosclerosis and end-organ arterial ischemia.

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