Cholesterol embolization syndrome

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Purpose of review

To describe cholesterol embolization syndrome (CES) and its risk factors, pathophysiology, clinical presentation, diagnosis and treatment.

Recent findings

To date, no specific diagnostic test (other than biopsy) for CES has been developed. Effective treatments for CES are yet to be developed.

Summary

CES (also referred to as cholesterol crystal embolization, atheromatous embolization or atheroembolism) occurs when cholesterol crystals and other contents of an atherosclerotic plaque embolize from a large proximal artery to smaller distal arteries causing ischemic end-organ damage. Clinical manifestations of CES include constitutional symptoms (fever, anorexia, weight loss, fatigue and myalgias), signs of systemic inflammation (anemia, thrombocytopenia leukocytosis, high erythrocyte sedimentation rate, elevated levels of C-reactive protein, hypocomplementemia), hypereosinophilia, eosononphiluria, acute onset of diffuse neurologic deficit, amaurosis fugax, acute renal failure, gut ischemia, livedo reticularis and blue-toe syndrome. CES may occur spontaneously or after an arterial procedure. There is no specific laboratory test for CES. Retinal exam demonstrating Hollenhorst plaques supports the diagnosis of CES. Biopsy of target organs (usually skin, skeletal muscles or kidneys) is the only means of confirming the diagnosis of CES. Treatment consists of supportive care and general management of atherosclerosis and arterial ischemia.

Keywords

atherosclerosis, cholesterol crystals, embolism, plaque

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Introduction

Cholesterol embolization syndrome (CES) – also referred to as cholesterol crystal embolization, atheromatous embolization or atheroembolism – occurs when cholesterol crystals and other contents of an atherosclerotic plaque embolize from a large proximal artery to smaller distal arteries causing end-organ damage [1••,2•].

Pathophysiology of CES is characterized by the following sequence of events: development of an atherosclerotic plaque in a large artery (such as the aorta, the internal carotid or iliac arteries); spontaneous or traumatic (including iatrogenic) plaque rupture; embolization of cholesterol crystals, platelets, fibrin and calcified debris from the plaque; mechanical plugging of small to medium (100–200 μm) arteries; and foreign-body inflammatory response to cholesterol emboli.

Cholesterol embolization syndrome is a manifestation of systemic atherosclerosis and is generally characterized by showers of microemboli. This is in contrast to a related syndrome of arterio-arterial thromboembolism in which there is commonly an abrupt release of one or a few large emboli made up of clot fragments originating from the surface of an atherosclerotic plaque [3]. Due to large particle size, arterio-arterial thromboembolism typically leads to occlusion of large arteries and severe ischemia.

Clinical presentation of CES is a combination of a nonspecific acute inflammatory response (e.g. fever, malaise, hypereosinophilia, eosinophiluria, elevated erythrocyte sedimentation rate) and manifestations specific to the arterial bed in which CES occurs (renal failure, gut ischemia, stroke, emboli to the skeletal muscles and the skin). Bluish discoloration of toes is a frequent dermatologic manifestation and the phrase blue-toe syndrome is often used synonymously with CES.

Historical developments

It is believed that CES was first described in 1844 by Fenger and colleagues in the Danish medical brochure *Ugeskrift for Laeger* (Doctors' Weekly). It was only after the report was translated into German in 1862 by the

Danish pathophysiologist Peter Ludvig Panum (1820–1885) that these initial findings were spread into the general medical literature [4].

Autopsy was the chief way of diagnosing CES [5] until the first ante-mortem noninvasive diagnosis was reported in 1961 by Dr Robert Hollenhorst (1913–2008), a Mayo Clinic ophthalmologist [6]. He described what will later be termed Hollenhorst plaques – highly refractive yellow cholesterol emboli at branching points of retinal arteries (Fig. 1).

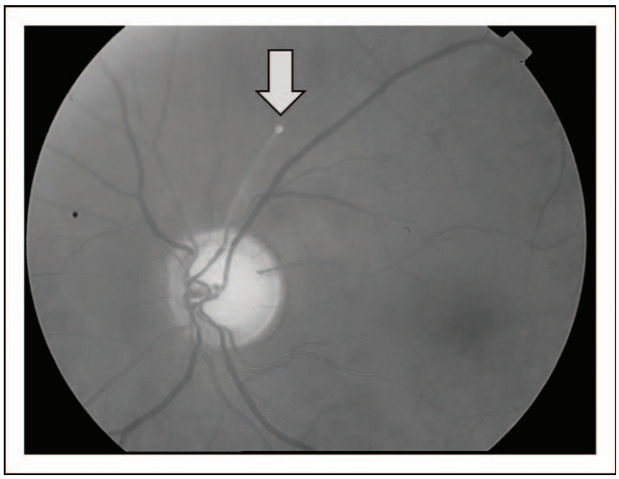
In 1976 blue-toe syndrome was first described [7]. And in 1990 an association between clinical syndromes of atheroembolism and aortic plaques seen on transesophageal echocardiography was first reported [8].

Pathophysiology

Cholesterol embolization syndrome is inextricably linked to the general development of atherosclerosis. Thus CES shares the same risk factors as general atherosclerosis including age, male sex, systemic hypertension, hypercholesterolemia, tobacco use, diabetes mellitus and family history.

Atherosclerotic plaques are located within the arterial intima and consist of an often necrotic core and a fibrous cap. The core contains foam cells (macrophages) and various lipids including low-density lipoprotein derived cholesterol crystals which become the source of cholesterol emboli. Cholesterol crystals reside deep inside the plaque and their formation is indicative of advanced atherosclerosis.

Figure 1 Hollenhorst plaque



Arrow points to cholesterol embolus (Hollenhorst plaque) in the retinal artery. Courtesy of Dr Irene Cherfas Tsyvine, Department of Ophthalmology, New Jersey Medical School, Newark, New Jersey, USA.

Key points

- Cholesterol embolization syndrome (CES; also referred to as cholesterol crystal embolization, atheromatous embolization or atheroembolism) occurs when cholesterol crystals and other contents of an atherosclerotic plaque embolize from a large proximal artery to smaller distal arteries causing ischemic end-organ damage.
- Clinical manifestations of CES include constitutional symptoms (fever, anorexia, weight loss, fatigue and myalgias), signs of systemic inflammation (anemia, thrombocytopenia leukocytosis, high erythrocyte sedimentation rate, elevated levels of C-reactive protein, hypocomplementemia), hypereosinophilia, eosinophiluria, acute onset of diffuse neurologic deficit, amaurosis fugax, acute renal failure, gut ischemia, livedo reticularis and/or blue-toe syndrome. These findings often occur after a vascular procedure in the aorta or its large branches.
- There is no specific laboratory test for CES. Retinal exam demonstrating Hollenhorst plaques supports the diagnosis of CES. Biopsy of target organs (usually skin, skeletal muscles or kidneys) is the only means of confirming the diagnosis of CES.
- There are no proven therapies for CES; treatment consists of supportive care and general management of atherosclerosis and arterial ischemia.

Cap rupture is sine qua non of cholesterol crystal embolization. The cap may be destabilized from within the plaque (e.g. inflammation or hemorrhage) or from its luminal side (e.g. shearing forces in systemic hypertension or traumatic disruption during vascular procedures).

Probably most plaque ruptures occur spontaneously. Iatrogenic plaque rupture leading to CES has been described following cardiac catheterization [9–11], cardiac surgery [12,13], angiography, vascular surgery [14,15] and percutaneous carotid interventions [16–18]. AQ2

It is unclear if thrombolytic or anticoagulant therapy is an independent risk of plaque rupture leading to CES. On the basis of retrospective systematic review of publications from 1980 to 2007, a causal relationship between CES and thrombolysis was hypothesized [19]. However, a subsequent small-scale prospective study could not confirm that thrombolysis is an independent cause of CES [20]. As for the anticoagulation therapy, it is unclear if CES is causally related to anticoagulants or it occasionally occurs in patients who happened to be on anticoagulation therapy.

Since there are no randomized clinical trials of thrombolytic or anticoagulant therapy whose primary outcome

was CES, one cannot either prove or disprove with certainty if such therapies lead to CES or not.

Sources of cholesterol emboli

Atheromatous aorta is the primary source of both cholesterol emboli and thromboemboli. A correlation between aortic atherosclerosis and the risk of CES was first noted in 1945 in an autopsy series [5]. The likelihood of finding atheroembolism was 1.3% in patients with moderate and 12.3% in patients with severe plaque erosion.

The abdominal aorta (whether normal in caliber or aneurismal) and the ileo-femoral arteries are the most common source of cholesterol emboli (Fig. 2) [21]. On the other end of the spectrum are the subclavian arteries which are a rare source of cholesterol emboli. Consequently, CES affecting upper extremities is rather unusual [22].

Embolization from atherosclerotic plaque in the aorta can occur not only in antegrade fashion but retrograde as well. This retrograde flow from the descending thoracic aorta into the aortic arch vessels can be demonstrated by magnetic resonance imaging (MRI) and Doppler echocardiography [23•]. In normal individuals, the flow in the descending aorta is exclusively antegrade during systole followed by a short period of flow reversal during early diastole. In patients with severe aortic regurgitation or patent ductus arteriosus, the duration of this flow reversal increases and may span the entire diastole (holodiastolic flow reversal).

Plaque imaging

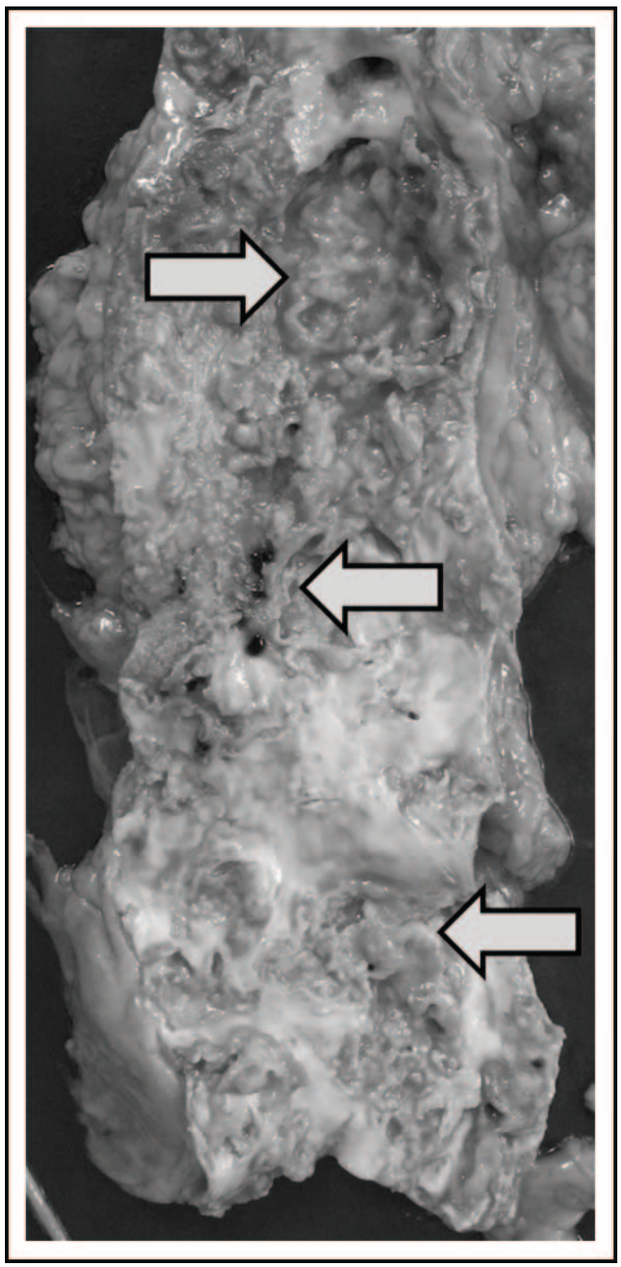
Atherosclerotic plaque in the aorta and its large branches may be visualized by ultrasound imaging techniques (Fig. 3); computed tomography (CT; Fig. 4), MRI (Fig. 5) [24] and aortography.

A correlation between aortic plaques visualized by 2D transesophageal echocardiography (TEE) and artero-arterial embolization phenomena was first reported in 1990 by Tunick and Kronzon [8]. Subsequent studies demonstrated that complex plaques ($\geq$4 mm in thickness) in the ascending aorta and the aortic arch are an independent risk factor for cerebral embolization [25–27]. Furthermore, in several case reports of biopsy-proven CES there were 2D TEE findings of complex plaques in the descending thoracic aorta [28,29]. The recently developed real-time 3D TEE provides detailed en face images of the aortic plaque (Fig. 6).

Inability to visualize the abdominal aorta past the origin of the superior mesenteric artery and the blind spot around the origin of the brachiocephalic artery are the major limitations of TEE (whether two-dimensional or three-dimensional) compared with CT and MRI.

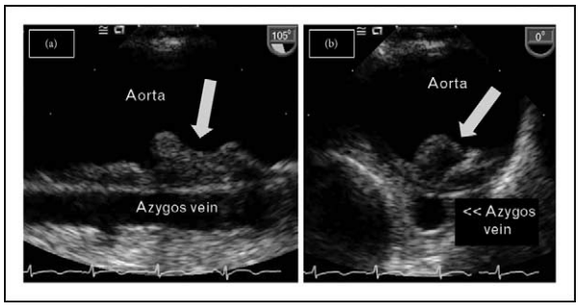
On occasion, aortic plaques may be visualized by transthoracic echocardiography or endoscopic ultrasound imaging of the upper gastrointestinal tract (Fig. 7)

Figure 2 Ulcerated plaque in the abdominal aorta



Arrows point to numerous complex atherosclerotic plaques in the abdominal aorta from a patient with CES. CES, cholesterol embolization syndrome. Courtesy of Dr Amy Rapkiewicz, Department of Pathology, New York University Langone Medical Center, New York, New York, USA.

Figure 3 Aortic plaque visualized by two-dimensional transesophageal echocardiography

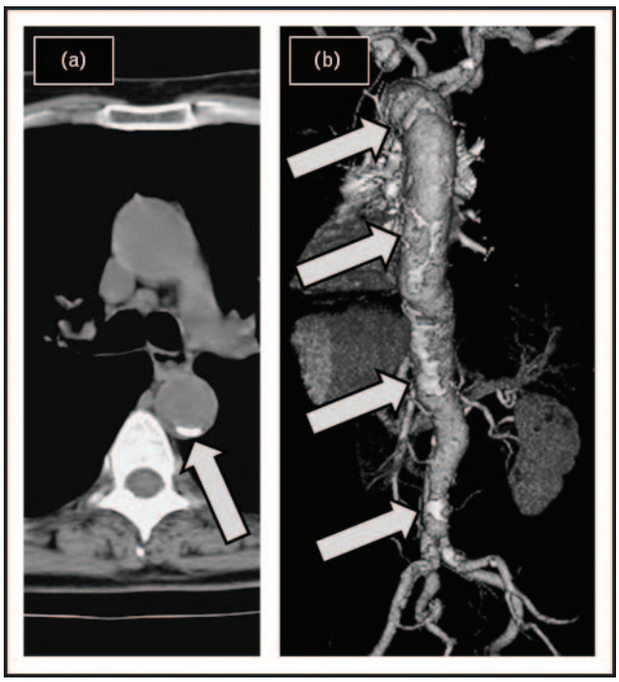


Arrows point to severe ulcerated plaque in the long (panel a) and the short axis (panel b) of the descending aorta. Muhamed Saric.

Contrast aortography has low sensitivity for detection of aortic plaques [30].

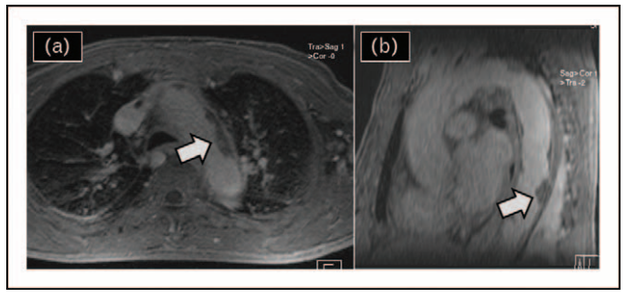
Irrespective of the imaging technique, often the index plaque that is the source of CES cannot be identified. Nonetheless, the presence of plaques is a marker of generalized atherosclerosis and supports the diagnosis of CES.

Figure 4 Aortic plaque visualized by computed tomography



Panel (a) demonstrates a calcified atherosclerotic plaque (arrow) on a axial cut of a two-dimensional chest CT. Panel (b) shows calcified atherosclerotic plaque throughout the visualized thoracoabdominal aorta (arrow) on a three-dimensional CT reconstruction. CT, compute tomography. Panel (a) courtesy of Dr Pierre Maldjian, Department of Radiology, New Jersey Medical School, Newark, New Jersey, USA. Panel (b) courtesy of Dr Robert Donnino, Division of Cardiology, New York University Langone Medical Center, New York, New York, USA.

Figure 5 Aortic plaque in the aorta visualized by MRI

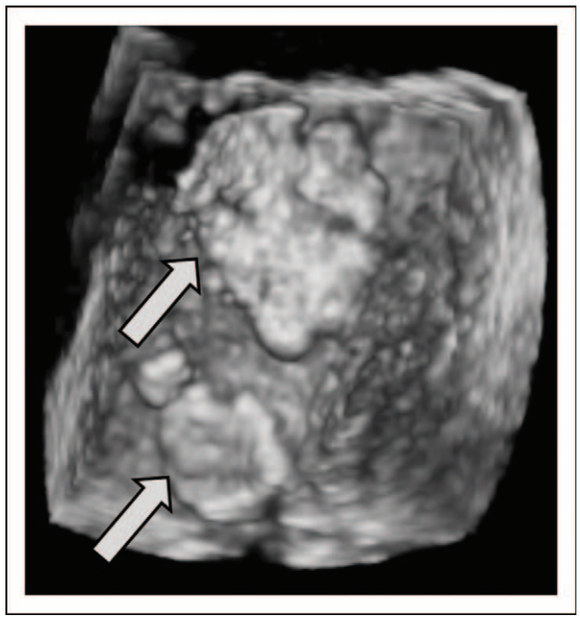


Arrows points to severe atherormatous plaque in the aortic arch (panel a) and the descending aorta (panel b) on MRI imaging in a patient who developed cholesterol embolization syndrome following cardiac catheterization. Courtesy of Dr M. Barbara Srichai-Parsia, Department of Radiology, New York University Langone Medical Center, New York, New York, USA.

Embolization of cholesterol crystals

After travelling through the arterial circulation, cholesterol crystals lodge in the arterioles and small arteries. In routinely processed biopsy specimens, cholesterol crystals are washed away; what remains are characteristic crescent-shaped clefts within the arterial lumen (Fig. 8). Cholesterol crystals *per se* can only be visualized in specially preserved specimens in which these crystals demonstrate birefringence under polarized light [31].

Figure 6 Aortic plaque shown on three-dimensional transesophageal echocardiography



Arrows point to severe plaque in the descending thoracic aorta visualized by three-dimensional TEE using the three-dimensional zoom technique. TEE, transesophageal echocardiography. Muhamed Saric.

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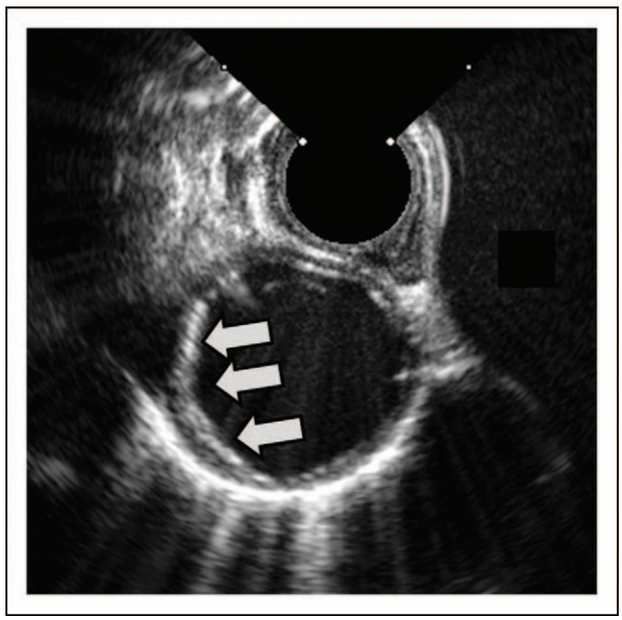
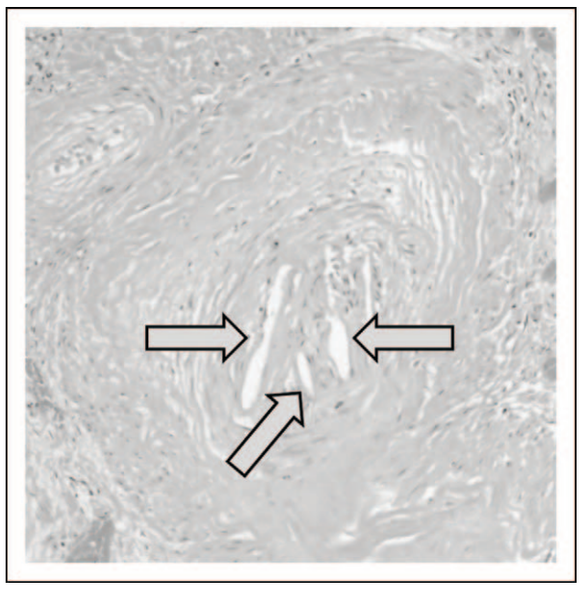
Figure 7 Aortic plaque visualized by endoscopic ultrasound



Arrows point to protruding plaque in the descending thoracic aorta. Courtesy of Dr Zamir Brelvi, Division of Gastroenterology, New Jersey Medical School, Newark, NJ.

Figure 8 Biopsy specimen from a patient with renal manifestations of cholesterol embolization syndrome



Arrows point to distinctive empty clefts within the lumen of a small renal artery in the kidney. Hematoxylin-eosin stain, original magnification ×200. Courtesy of Dr Amy Rapkiewicz, Department of Pathology, New York University Langone Medical Center, New York, New York, USA.

In addition to mechanically occluding the small arteries, cholesterol crystals also trigger an inflammatory response which consists of foreign body reaction and intravascular thrombus formation followed by endothelial proliferation and eventually fibrosis. Cholesterol emboli may remain lodged for months [32]. The net result of cholesterol crystal embolization is partial or complete occlusion of target arteries leading to tissue ischemia.

Clinical presentation

The exact incidence and prevalence of CES is unknown since there is no definitive test for the diagnosis of CES other than a biopsy. CES is usually characterized by repetitive showers of microemboli to a variety of tissues and organs. Probably a large number of CES episodes never become clinically apparent. Clinical presentation of CES is a combination of a systemic inflammatory response and signs and symptoms specific to end-organ damage.

Inflammatory response

The inflammatory response often manifests clinically as fever, anorexia, weight loss, fatigue and myalgias. Laboratory test may show anemia, thrombocytopenia leukocytosis, high erythrocyte sedimentation rate, elevated levels of C-reactive protein and hypocomplementemia.

Hypereosinophilia (6–18% of the total leukocyte count) and eosinophiluria are a frequently observed, albeit a non-specific, sign of CES. Hypereosinophilia may occur in up to 80% of the patients with CES and is often observed only during the first few days of CES [33]. The exact mechanism of hypereosinophilia in CES is not known [34].

Skin manifestations

The reported frequency of skin findings in CES ranges from 35 to 96%. The highest rates have been reported in patients with concomitant renal manifestations of CES [35]. Skin findings include livedo reticularis (49% of patients with skin manifestations), gangrene (35%), cyanosis (28%), ulceration (17%), nodules (10%) and purpura (9%). Skin findings are most often seen on the lower extremities. Less frequently they occur on the trunk and rarely on the upper extremities [36].

Venous plexuses filled with deoxygenated blood give rise to livedo reticularis, a collection of reddish blue spots laid in a fishnet pattern. Although commonly seen in CES, livedo retucularis is not pathognomonic for CES. It can also be seen in polyarteritis nodosa, systemic lupus

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erythematosus or following the use of potent vasoconstriction agents.

In the lower extremities, CES often leads to sudden development of purple or blue discoloration of toes and/or other regions of the foot [22]. Although the term 'blue-toe syndrome' was first described in the context of CES [7], it may also be seen in vasculitis, antiphospholipid syndrome, hyperviscocity states and endocarditis [37]. These skin changes are merely a reflection of microvascular ischemia.

Toe and foot cyanosis is frequently more visible in dependent leg areas, may blanch with moderate pressure and often has asymmetric distribution (one leg may be more affected than the other). With marked microvascular ischemia, tissue necrosis develops and potentially leads to ulcerations and gangrene.

Because cholesterol emboli occlude small arteries and arterioles rather than large superficial arteries, distal pulses frequently remain palpable in CES. However, absent peripheral pulses do not exclude the diagnosis of CES as such patients frequently have other manifestations of advanced atherosclerosis including peripheral arterial occlusive disease.

Renal manifestations

Cholesterol crystal embolization to the kidneys – also referred to as atheroembolic kidney disease – primarily affects the arcuate and interlobar renal arteries (Fig. 8). Rarely, the cholesterol crystals embolize to the afferent arteries and glomeruli. Because cholesterol crystal embolization has patchy distribution, renal biopsies may be negative for CES [38].

Cholesterol embolization syndrome has been shown to account for about 7% of all cause of acute renal insufficiency in a series of 259 patients aged 60 years or older who underwent renal biopsy. This study also underscores how difficult it may be to establish the diagnosis of CES using only clinical data. Prebiopsy clinical diagnosis of CES was correct in only one-sixth of these patients [39].

Primary manifestations of renal CES include elevation of serum creatinine, proteinuria and accelerated and hard-to-control systemic hypertension [40,41]. Renal CES can lead to acute, subacute and chronic kidney failure.

Acute and subacute forms are usually caused by a sudden massive shower of cholesterol emboli (e.g. after a vascular procedure), whereas chronic forms often result from spontaneous low-level cholesterol crystal embolization over extended periods of time.

On the one end of the spectrum, kidney damage following CES may resolve spontaneously, whereas on the other extreme the patient may become dialysis-dependent [42].

Gastrointestinal manifestations

The reported incidence of gastrointestinal manifestations ranges from one fifth to about one half of all patients with CES [43]. Gut ischemia is the primary manifestation of CES in the gastrointestinal tract which may lead to intestinal blood loss (often from microscopic mucosal erosion that can easily be missed by endoscopic or radiologic studies) [44], pseudopolyp formation, ulceration and intestinal perforation [45]. Less common gastrointestinal manifestations CES may include acalculous necrotizing cholecystitis [46] and acute pancreatitis in the elderly patients [47].

Neurologic manifestations

Spontaneous or traumatic release of showers of cholesterol emboli originating in the thoracic aorta or carotid and vertebral arteries may lead to neurologic complications of CES. Typically, CES leads to diffuse brain injury (characterized by confusion and memory loss) rather than focal neurologic deficits. Neurologic manifestations of CES are predominantly due to small ischemic lesions and border zone infarcts [48].

Microemboli in cerebral arteries – including cholesterol crystals – can be detected by transcranial Doppler (TCD) ultrasonography as high-intensity transient signals (HITS) superimposed on standard spectral Doppler flow velocity recordings. HITS are not pathognomonic for cholesterol crystals emboli as they may also be seen with microembolization of fat, air and calcium particles. Myriads of HITS can be demonstrated by TCD during carotid endarterectomy, carotid angioplasty [49], and coronary artery bypass grafting (especially during aortic clamping) [50].

Ocular manifestations

Cholesterol crystal emboli from the thoracic aorta and the carotids may lead to retinal artery occlusion. These emboli are seen on fundoscopy as highly refractive yellow particles at branching points of retinal arteries and are termed Hollenhorst plaques. Typically, ocular CES presents clinically as amaurosis fugax.

Diagnosis

Cholesterol embolization syndrome should be suspected in any patient (frequently an elderly man) with any of the following:

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(1) Constitutional symptoms (fever, anorexia, weight loss, fatigue and myalgias)
(2) Signs of systemic inflammation (anemia, thrombocytopenia leukocytosis, high erythrocyte sedimentation rate, elevated levels of C-reactive protein, hypocomplementemia)
(3) Hypereosinophilia and eosinophiluria
(4) Acute onset of diffuse neurologic deficit, amaurosis fugax, acute renal failure, gut ischemia, livedo reticularis and/or blue-toe syndrome
(5) Recent history of a vascular procedure in the aorta or its large branches
(6) Retinal exam demonstrating Hollenhorst plaques

Histopathologic diagnosis is the only test for confirming the diagnosis of CES [51]. Skin skeletal muscles or the kidneys are the usual biopsy locations. Since poor healing at the sampling site has been observed, biopsies in CES should be performed with caution.

Treatment

Since CES is a manifestation of atherosclerosis, risk factors modification should be an integral part of CES treatment including cessation of tobacco use, lowering of serum cholesterol and control of hypertension and diabetes mellitus. There is still no specific therapy for CES [52]. Treatment consists of supportive care and secondary prophylaxis against further episodes of CES [53].

There is no evidence that anti-inflammatory treatments are beneficial in CES. Although there is also no direct evidence that antiplatelet agents and angiotensin-converting enzyme (ACE) inhibitors directly prevent the recurrence of CES, their use seems reasonable as they have been shown to prevent other adverse cardiovascular events including myocardial infarction, the leading cause of death in patients with atherosclerosis [54–56].

One should probably not initiate thrombolytic or anticoagulant therapy in patients with CES given the unresolved issue of whether such agents precipitate CES or not. However, if there is a separate indication (such as the presence of a mechanical prosthetic valve or atrial fibrillation), anticoagulation should probably be continued [57].

Surgical therapy (such as endarterectomy, vessel ligation or bypass) or percutaneous interventions (e.g. endoluminally placed stent grafts) may decrease the rate of further embolism [58–60].

Conclusion

Cholesterol embolization syndrome is a manifestation of advanced atherosclerosis that leads to high morbidity and mortality. It is a form of arterio-arterial embolism in which contents of a ruptured plaque in the aorta or a large proximal artery embolize to distal small to medium-sized arteries. This leads to ischemic end-organ damage through a combination of mechanical plugging and inflammation in the target arteries.

Because there are no clinical or laboratory findings that are specific for CES, a high degree of clinical suspicion is required in establishing the diagnosis. Biopsy (demonstrating either clefts or birefringent cholesterol crystals) is the only means of confirming the diagnosis of CES ante mortem. Unfortunately, there is no specific therapy for CES; treatments are directed toward general management of atherosclerosis and arterial ischemia.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest for M.S.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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