Cholesterol Emboli

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Abstract

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Cholesterol emboli syndrome (CES) is a rare and often devastating multi-organ disease resulting in variable, nonspecific clinical findings that make diagnosis difficult, requiring a high index of suspicion. Cholesterol emboli originate from complex atheromatous plaque found in large caliber proximal arteries primarily in the aorto-iliac-femoral system. Plaque rupture results in distal embolization of plaque debris, including cholesterol crystals, that become lodged within smaller caliber arteries and arterioles resulting in mechanical obstruction and a provoked inflammatory response that leads to end-organ damage.

Multiple organs can be affected by cholesterol emboli including the brain, gastrointestinal tract, kidney, and skin that can manifest with a variety of clinical findings such as encephalopathy, gastrointestinal bleeding, renal failure, and “blue toes.” Plaque rupture can be spontaneous or result from aortic manipulation during catheterization-based procedures or vascular surgery. Treatment remains largely supportive and includes risk factor modification, statin therapy, general avoidance of anticoagulants and thrombolytic agents, and surgical or endovascular procedures to exclude sources of cholesterol emboli.

Keywords

Atherosclerosis
Atheroma
Blue toe syndrome
Cholesterol crystals
Cholesterol emboli
Hollenhorst plaques
Plaque rupture

Introduction

Cholesterol embolization syndrome (CES
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) refers to the arterio-arterial embolization of plaque debris (predominantly cholesterol crystals) from an atheroma within proximal large caliber arteries, typically in the aorto-iliac-femoral system, to small, distal arteries and arterioles. This results in nonspecific constitutional symptoms and end-organ damage secondary to mechanical obstruction and a provoked inflammatory reaction [1]. Within the medical literature, several terms are synonymous with cholesterol embolization syndrome including atheroembolism, atheromatous embolization, cholesterol embolization, and cholesterol crystal embolization.

Cholesterol embolization is a rare disease that often presents insidiously secondary to the showering of microemboli into smaller distal arteries. This must be distinguished from the related but more common arterio-arterial thromboembolism that results from the acute embolization of larger fragments originating from thrombus overlying a complex atheromatous plaque, which can result in the sudden occlusion of larger downstream arteries with development of severe, acute ischemia [2].

The pathophysiology of CES consists of six key elements: presence of complex atherosclerotic plaque, plaque rupture, distal embolization of plaque debris, lodging of microemboli within distal arteries, foreign body reaction, and end-organ damage. CES can potentially affect any organ system resulting in a wide array of clinical manifestations. The clinical presentation, diagnosis, and management of CES will be reviewed.

History

The first report of CES is believed to have occurred in 1844 by Fenger and colleagues in the Danish medical brochure Ugeskrift for Læger (Doctors' Weekly) with the autopsy description of Bertel Thorvaldsen, a Danish/Icelandic sculptor [3]. In 1862, this description was translated into German and made available to a wider medical audience [4]. The first autopsy series to provide a detailed description of the diffuse nature and multi-organ involvement of CES was published in 1945 from New York Hospital [5]. Then in the 1950s, the first observation of cholesterol crystals within the arteries of affected organs from frozen pathological specimens was described using polarized light microscopy [6]. To this day, biopsy remains the gold standard for definitive diagnosis of CES.

In 1957, Thurlbeck and Castleman were the first to report CES as a complication of vascular surgery [7]. This was followed by the classic description of pathognomonic retinal plaques in 1961 by Hollenhorst, an ophthalmologist from Mayo Clinic [8]. The blue toe syndrome was first described in 1973 by Karmody and later became synonymous with cholesterol embolization [9]. It was not until 1990 that the association between atheromatous aortic plaque visualized on transesophageal echocardiography (TEE) and clinical manifestations of CES; this significantly evolved our understanding of the underlying pathophysiology of CES [10].

Pathophysiology

The pathophysiology of CES consists of six key elements [1]:

1. The presence of atherosclerotic plaque in a proximal, large caliber artery (this can include the aorta, carotid arteries, iliac arteries, or femoral arteries)

2. Plaque rupture

3. Distal embolization of plaque debris including cholesterol crystals
4. Lodging of emboli into smaller caliber vessels leading to partial or complete occlusion
5. Foreign body inflammatory response to the cholesterol crystals
6. End-organ damage secondary to the combination of mechanical occlusion and the local inflammatory response

Atherosclerotic Plaque in a Proximal Artery

The development of generalized atherosclerosis is a lifelong process that begins in childhood and progresses to more advanced stages later in life. Histologically, atherosclerosis is localized to the arterial intima. In childhood to early adulthood, precursor lesions begin to form in the intimal layer that are characterized by fatty streaks containing layers of macrophage foam cells in combination with intracellular and extracellular lipid droplets. These clinically silent lesions then progress to more advanced stages overtime becoming more prevalent in the middle-aged and elderly. Once a lipid core develops, the lesion progresses through various histological stages of increasing complexity from an atheroma to fibroatheroma to a complex plaque associated with plaque hemorrhage, fissure, and ulceration, as well as development of overlying thrombus. These more advanced plaques can also develop calcifications. It is these advanced lesions that provide the source of cholesterol crystals for embolization in CES [11]. The histopathologic stages of atherosclerotic plaque are summarized in Table 27.1 .

Table 27.1

Stages of atherosclerotic plaque

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Stage	Lesion classification	Histology	Age at onset	Clinical manifestation
I	Initial	Isolated macrophages, foam cells	Childhood and adolescence	Clinically silent
II	Fatty streak	Intimal fatty streak, intracellular lipid accumulation		
III	Intermediate	Stage II lesion with developing extracellular lipid pools		
IV	Atheroma	Developing extracellular lipid core	Fourth decade into advanced age	Clinically silent or overt
V	Fibroatheroma	Stage IV lesion with overlying fibrotic cap		
VI	Complicated plaque	Stage V lesion with evidence of fibrotic cap defect, hematoma/hemorrhage within lipid core, thrombus		

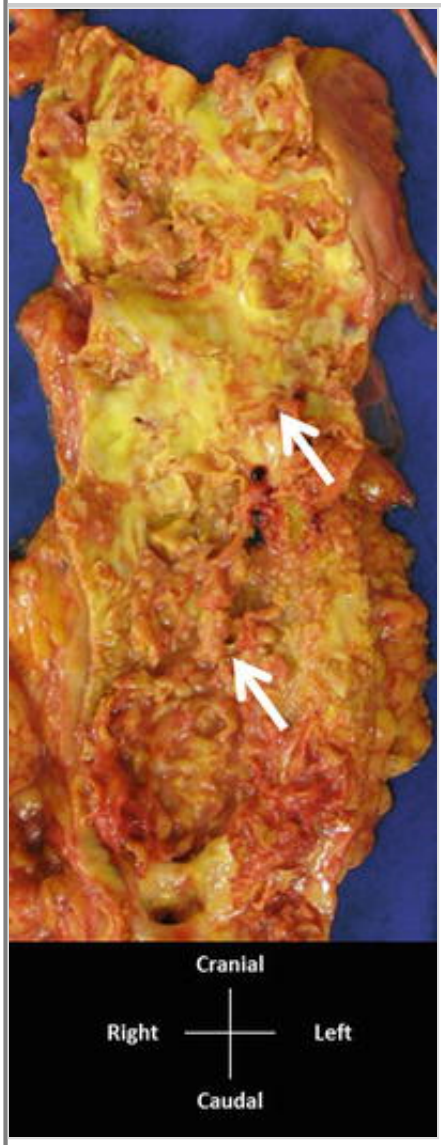
Based on data from Stary et al. [11]

An advanced atheromatous plaque is composed of a necrotic core with an overlying fibrous cap (Fig. 27.1). The necrotic core contains cellular debris, macrophage foam cells, and various lipids. The foam

cells contain oxidized low-density lipoprotein that is released into the extracellular space upon cell death. This cholesterol-rich material provides the primary source for cholesterol emboli. Cholesterol within a plaque can exist either in a soluble form or a crystalline form. Cholesterol crystals are typically found deep within the necrotic core of the plaque and represent more advanced atherosclerosis. Crystalline cholesterol can account for more than 40 % of the total cholesterol contained within a plaque [12]. The fibrous cap of a plaque is composed of endothelial cells, smooth muscle cells, and connective tissue.

Fig. 27.1

Gross pathologic specimen of aortic atherosclerosis. The abdominal aorta is cut lengthwise to reveal severe advanced atherosclerosis (*arrow*)



In the context of echocardiographic and radiologic imaging, atheromatous plaque is often classified as simple or complex. Simple plaques appear as smooth border lesions within the arterial luminal wall that have a wall thickness < 4 mm with absence of any mobile components. Complex plaques have a wall thickness ≥ 4 mm often with irregular, ulcerated luminal borders and evidence of mobile components consistent with overlying thrombus.

Simple plaques have an intact fibrous cap that prevents communication between the cholesterol-rich

necrotic core and the arterial lumen. Complex plaques often have disruption of the fibrous cap either by fissuring, ulceration, or rupture that exposes the plaque contents to the arterial lumen, thereby creating a potential source for cholesterol emboli. The aorto-iliac-femoral arterial system is the primary location of atheromatous plaques, and thus CES typically localizes to arterial beds of the abdomen and the lower extremities. In contrast, atheroembolism in the upper extremities is uncommon [13].

The risk of embolization is directly related to the presence, severity, and extent of atherosclerosis. This association was first shown in the previously mentioned autopsy series from the late 1940s. Among patients without significant atherosclerotic disease, no CES was observed. However, in patients with aortic plaques, the risk of atheroembolism increased linearly with increasing severity of atherosclerotic disease; moderately eroded plaques were associated with a 1.3 % incidence of atheroembolism and severely eroded plaques with an increased incidence of 12.3 % [5].

Imaging of the Aorta

Aortic plaques can be visualized, characterized, and quantified by a variety of imaging modalities including transesophageal echocardiography (TEE), computed tomography (CT), and magnetic resonance imaging (MRI) [14]. TEE, predominantly two dimensional (2D), is typically the first-line imaging technique for the detection and measurement of aortic plaque (Fig. 27.2) [1]. The association between clinical embolization and advanced aortic atherosclerotic plaque visualized on TEE was first reported in 1990 [10]. Further studies later confirmed that aortic plaque detected by TEE represents a potential source for systemic emboli [15–17]. Noncalcified complex atheromas in the ascending aorta and aortic arch correlated with a higher risk where a plaque thickness ≥4 mm measured on TEE emerged as a clinically important predictor of increased vascular embolic events [17–19]. These embolic events could have represented both arterial thromboembolism and atheroembolism. However, additional case reports with biopsy-proven CES found an association with complex aortic atheromas visualized on TEE, thereby strengthening not only the role of the aortic plaque in CES but also the role of TEE in detecting these plaques [20]. Real-time three-dimensional (3D) TEE is a newer imaging technique that may provide additional morphological detail of the plaque and could have an increasing clinical role in the future [21].

Fig. 27.2

2D and 3D TEE imaging of aortic plaque. (**a**, **b**) 2D TEE comparison of normal aortic arch (**a**) and severe ulcerated plaque (*arrows*) in the aortic arch. (**c**, **d**) 3D TEE demonstrates absence (**c**) and presence of severe atherosclerotic plaque (*arrows*) in the aortic arch

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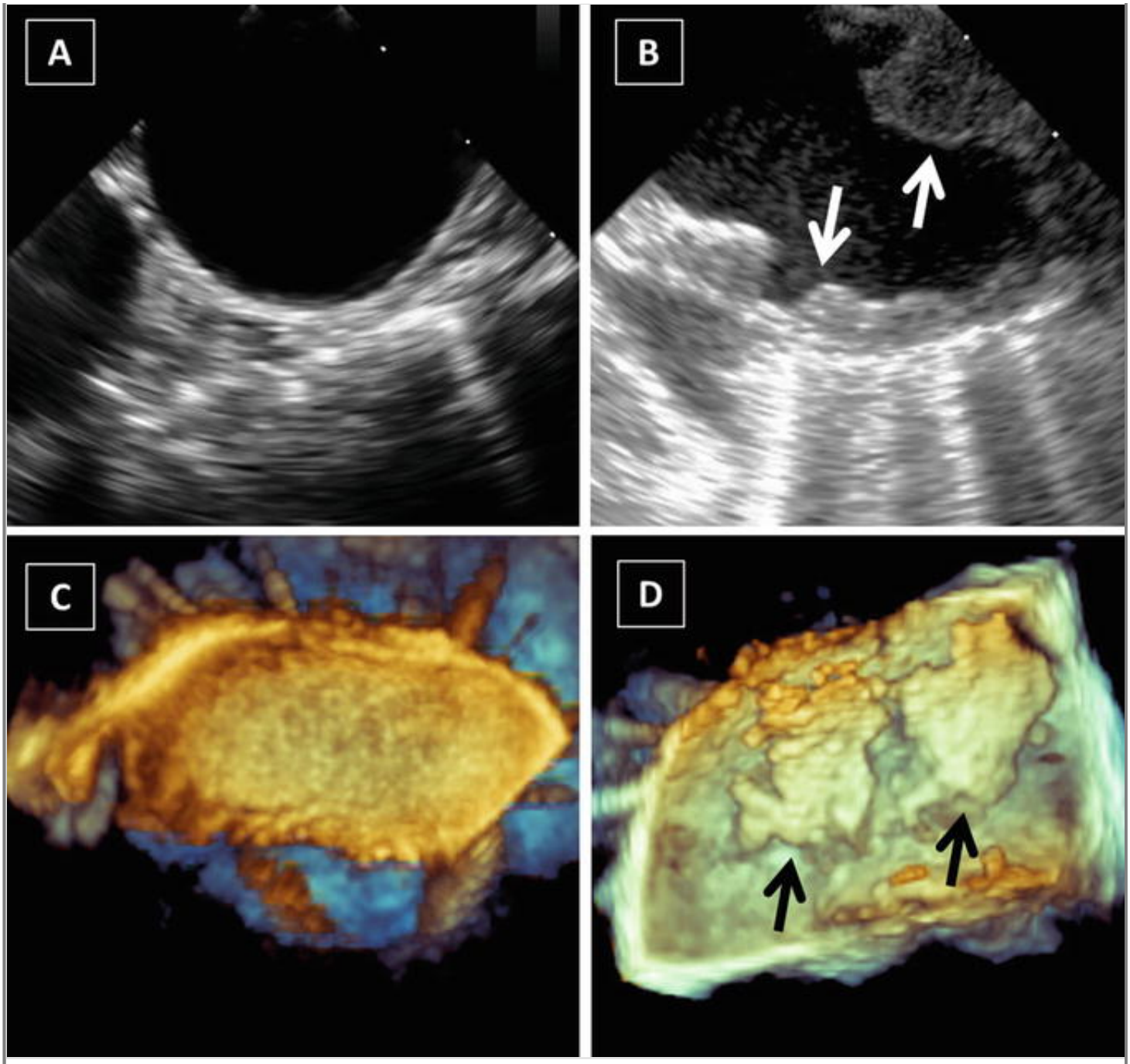

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CT and MRI are additional imaging techniques that can be considered for detection and characterization of aortic plaque that may provide a less invasive and more comprehensive evaluation of aortic atherosclerosis relative to 2D TEE (Figs. 27.3 and 27.4) [22–24]. For imaging of the major branches of the thoracic aorta, CT and MRI are superior to TEE as TEE has a blind spot around the origin of the brachiocephalic artery due to interposition of the air-filled bronchi between the esophagus and the artery. In addition, the abdominal aorta is incompletely visualized on TEE as it is limited to the proximal abdominal aorta between the diaphragm and origin of the superior mesenteric artery. Therefore, for complete visualization of the aorta-iliac-femoral arterial system, CT or MRI is preferred.

Fig. 27.3

CT imaging of aortic plaque. 2D CT (**a**, **b**) and 3D CT (**c**, **d**) imaging of atherosclerotic plaque in the

aorta. (**a**) Coronal cut demonstrates severe calcified atherosclerotic plaque in the aortic arch (*arrow*). (**b**) Severe calcified plaque is seen in the entire abdominal aorta and its iliofemoral branches (*arrows*). (**c**, **d**) 3D-reconstructed CT images show diffuse focal plaque in the thoracic and abdominal aorta (*arrows*) (Courtesy of Dr. Robert Donnino, Veterans Affairs New York Harbor Healthcare System, New York, NY, and Departments of Medicine and Radiology, New York University School of Medicine, New York, NY)

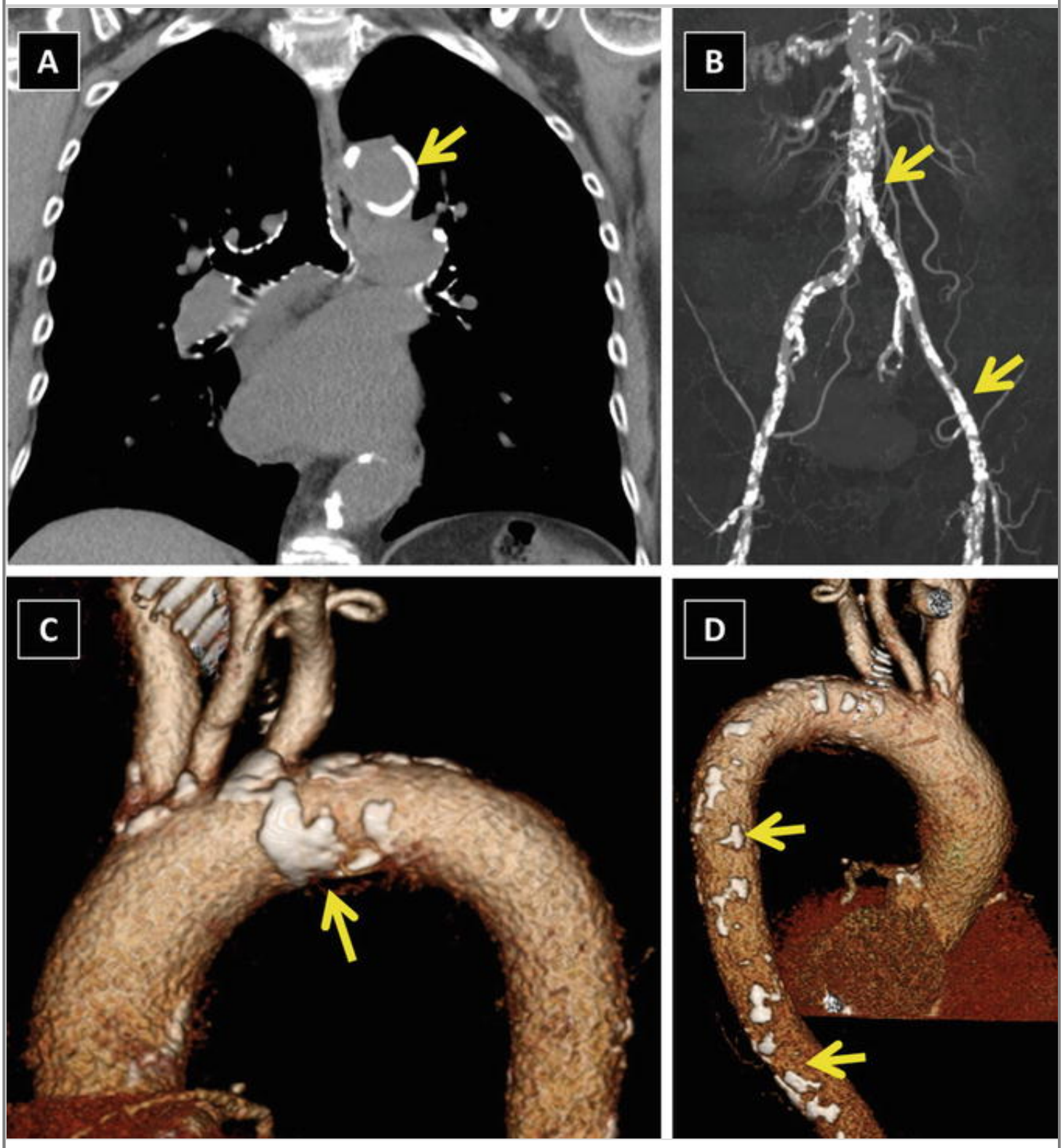
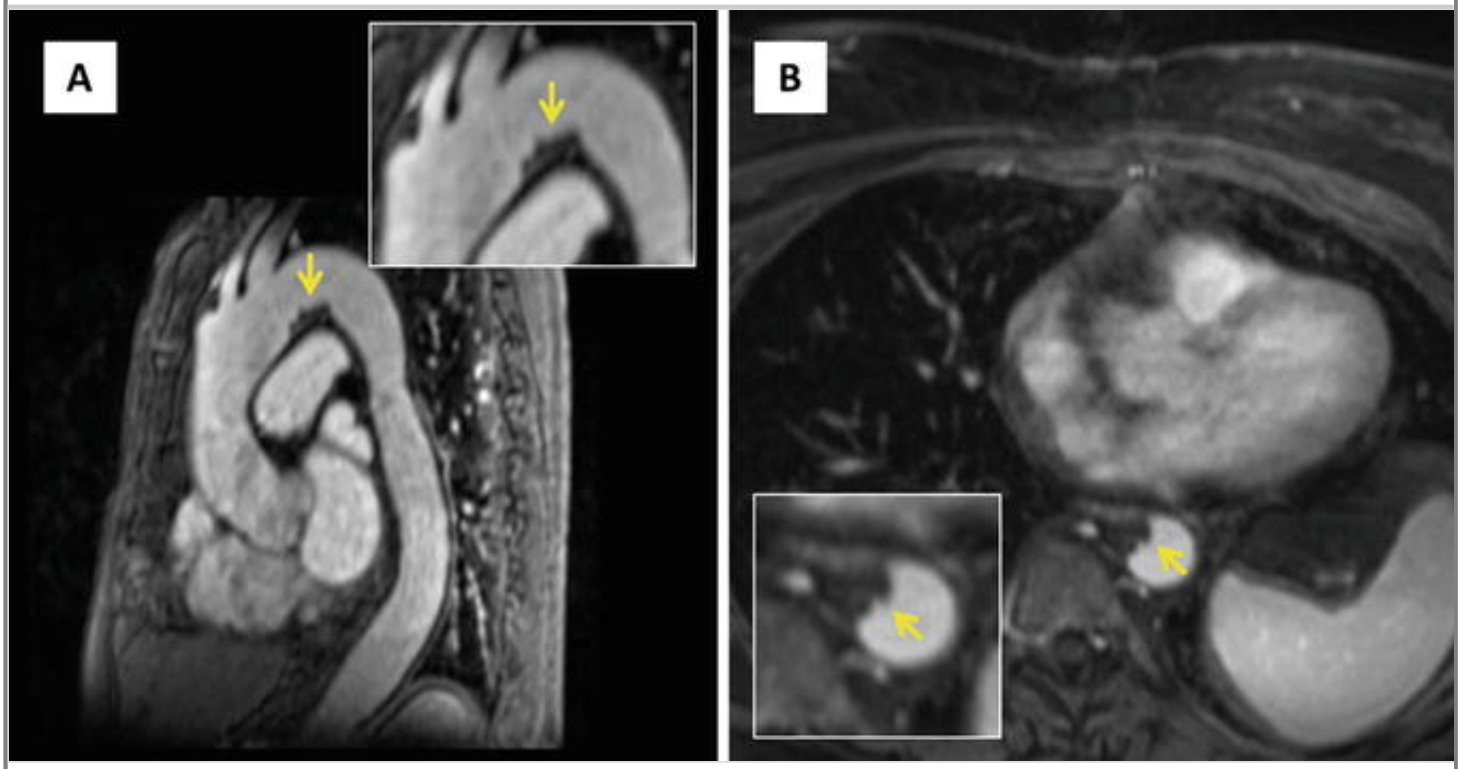


Fig. 27.4

MRI imaging of aortic plaque. (**a**) Magnetic resonance angiography (MRA) demonstrates a prominent ulcerated plaque (*arrow*) in the inferior aspect of the aortic arch in a near-sagittal cut. (**b**) MRA shows a protruding ulcerated plaque in the descending aorta (*arrow*) in an axial cut (Courtesy of Robert Donnino, Veterans Affairs New York Harbor Healthcare System, New York, NY, and Departments of Medicine and Radiology, New York University School of Medicine, New York, NY)



Conventional arteriography has a low sensitivity for aortic plaque detection and often fails to detect plaques that are identified on other imaging modalities. In addition, arteriography is invasive and could lead to mechanical disruption of an aortic plaque and subsequent arterial cholesterol embolization or thromboembolism and, therefore, should generally be avoided [25].

Plaque Rupture

Rupture of the fibrous cap is a necessary event in the development of CES. This exposes the cholesterol-rich core of the atherosclerotic plaque to the arterial lumen. Plaque rupture can either be spontaneous or traumatic. Traumatic plaque rupture can be secondary to mechanical disruption from intra-arterial manipulation during catheter or surgical procedures. It remains controversial whether or not thrombolytic or anticoagulant therapy is an independent risk factor for plaque rupture and cholesterol embolization.

Spontaneous Atheroembolism

Spontaneous rupture of an aortic plaque shares similar mechanistic features to plaque rupture in other arterial beds. Plaque composition rather than plaque size is thought to play the principal role in plaque vulnerability. More vulnerable plaques often have larger lipid cores and thinning of fibrotic caps mediated by a complex interaction between inflammatory and extracellular matrix cells. Therefore,

inflammation may play a critical role in altering plaque composition and thus increasing a plaque's vulnerability to spontaneous rupture [26].

The rate of spontaneous aortic plaque rupture in the general population has been extrapolated from older pathoanatomic series that were published in the era before the widespread use of intra-arterial cannulation for diagnostic and therapeutic purposes; this estimated rate ranged from <1 to 3.4 % [5, 27, 28]. However, the incidence of spontaneous plaque rupture leading to CES remains low even among higher-risk populations. One antemortem retrospective study of 519 patients with complex aortic plaque diagnosed by TEE found CES to occur at a rate of 1 % over a 3-year follow-up. For comparison, this CES rate is significantly lower than the 20 % rate of arterial thromboembolism observed in the same cohort [29].

Traumatic Plaque Rupture

Traumatic aortic plaque rupture can occur following intra-arterial manipulation during catheterization or cardiovascular surgery. Although cholesterol embolization has been reported in association with cardiac catheterization, it is considered a rare complication. The reported incidence of clinically apparent CES after cardiac catheterization is <2 % [30–32]. The data remains inconclusive regarding whether or not radial access versus femoral access results in a lower incidence of this complication [30, 33]. CES, particularly cerebral atheroembolism, has been a major concern following transcatheter aortic valve replacement (TAVR) with early registries reporting an incidence of 2.4–4 %. However, the incidence seems to be declining with the use of smaller catheters and more stringent patient selection criteria. The routine use of intra-arterial embolic protection devices may lead to an even further decline in embolization events [34].

CES in association with cardiovascular surgery is also rare. Risk is directly correlated with extent and severity of atherosclerosis in the ascending aorta. CES has been reported more frequently in association with coronary revascularization than valvular operations [35]. Off-pump cardiovascular surgeries may lead to less embolic events compared to the use of cardiopulmonary bypass techniques [36]. CES has also been a rare complication associated with carotid endarterectomy, carotid stenting, and abdominal aorta procedures including endovascular aneurysm repair (EVAR) [37–39].

Thrombolytic and Anticoagulation Therapy

The incidence of intra-plaque hemorrhage and an associated increase in plaque rupture leading to CES as a consequence of thrombolytic or anticoagulation therapy remains controversial. Case reports have suggested that CES can develop subsequent to thrombolytic therapy given for the acute management of various conditions including myocardial infarction and deep venous thrombosis. Although a small prospective trial of post-myocardial infarction patients treated with or without thrombolytic therapy failed to demonstrate a relationship [40], there still exists a controversy [41]. Similarly, case reports have suggested that anticoagulation is also associated with an increase in CES and that discontinuation of therapy can lead to clinical improvement [42, 43].

In addition to warfarin, the novel anticoagulants have also been suggested to play a role in development of CES [44]. However, it is difficult to determine if this is a causal relationship or merely an association. At this time, no randomized trials have specifically evaluated anticoagulation as an independent risk factor for development of CES. There is limited literature to support that the use of anticoagulation in patients with concurrent CES is safe and feasible among patients with a separate indication for anticoagulation [45]. Therefore, per current evidence, the causal relationship between cholesterol embolization and the use of anticoagulation and/or thrombolytic therapy can neither be proven nor

refuted. Based on this unresolved controversy, routine use of anticoagulation among patients with CES is not generally recommended. However, use of anticoagulation in CES appears reasonable in patients with a separate indication for anticoagulation including atrial fibrillation, left ventricular thrombus, or mechanical prosthetic valve [1].

Embolization of Plaque Debris

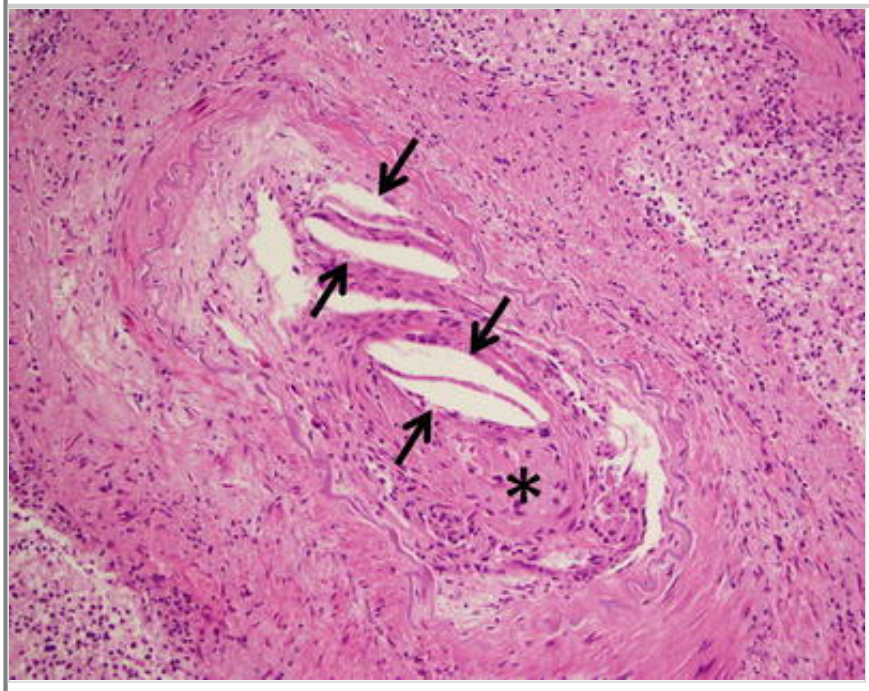
Plaque rupture is thought to lead to a showering of plaque debris including cholesterol crystals to a variety of distal tissue and organs. Showering of microemboli typically occurs slowly overtime and may not become clinically apparent until significant end-organ damage has occurred. This is in contrast to arterial thromboembolism where a large thrombus embolizes all at once. Currently, there are no diagnostic tests to definitively detect cholesterol microembolization in the absence of clinical findings; therefore, it is possible that there are many cases of silent cholesterol plaque embolization.

Lodging of Emboli into Smaller Caliber Vessels

Once released from a plaque, cholesterol crystals travel through the arterial circulation until they reach smaller caliber arteries or arterioles where they become lodged within their lumens. In routine biopsy specimens, cholesterol crystals are not visualized directly because they are washed away during standard specimen processing. However, characteristic ovoid or crescentic clefts within the lumens of the affected vessels can be seen; they represent voids in which the crystals had previously been located (Fig. 27.5) [46]. Direct visualization of cholesterol crystals is also possible if the biopsy specimen is preserved with liquid nitrogen then viewed with polarized microscopy; the crystals will demonstrate birefringence (double refraction of polarized light) [6].

Fig. 27.5

Cholesterol clefts on histopathology. A hematoxylin-eosin-stained section of a small renal artery demonstrates several pathognomonic empty spaces referred to as cholesterol clefts (*arrows*) within the partly fibrosed (*asterisk*) lumen. Magnification 200× (Courtesy of Dr Amy Rapkiewicz, Department of Pathology, New York University Medical Center, New York, NY)



Inflammatory Response

In addition to mechanical obstruction, cholesterol emboli incite an inflammatory reaction. This response has been well documented in an animal model and consists of three phases: acute inflammation, foreign body reaction with intravascular thrombus formation, and endothelial proliferation and fibrosis. The acute inflammatory stage is marked histologically by local infiltration of polymorphonuclear cells and eosinophils. Over the following 24–48 h, the cholesterol crystals elicit a foreign body response leading to infiltration of mononuclear cells and their transformation into giant cells that phagocytizes the cholesterol crystals. Simultaneously, thrombus develops in the arterial lumen. In the final stages, there is a proliferation of endothelial cells within the wall of the affected vessel with an eventual progression to intravascular fibrosis that leads to long-term stenosis or complete obliteration of the artery. This results in tissue ischemia and necrosis manifested as end-organ damage [47].

End-Organ Damage

The mechanical obstruction and inflammatory response provoked by cholesterol emboli can affect virtually any organ. However, clinically CES is most apparent when the brain, kidney, gastrointestinal tract, and skin are affected. The end-organ manifestations seen within these tissues are further described.

Central Nervous System

Cholesterol emboli released from advanced atherosclerotic plaques within the ascending aorta, aortic arch, carotid arteries, and vertebral arteries can enter the central nervous system circulation. These atheroemboli can either result from spontaneous plaque rupture or from mechanical manipulation during intra-arterial catheter-based procedures or cardiovascular surgeries, as previously described. Showering of atheroemboli into the cerebral circulation can result in diffuse brain injury that is often characterized by global symptoms of confusion and memory loss rather than focal neurological deficits that are more typically seen with arterial thromboembolism [48]. Brain imaging can demonstrate multiple small areas of infarction in different vascular territories and/or border zone infarctions [49].

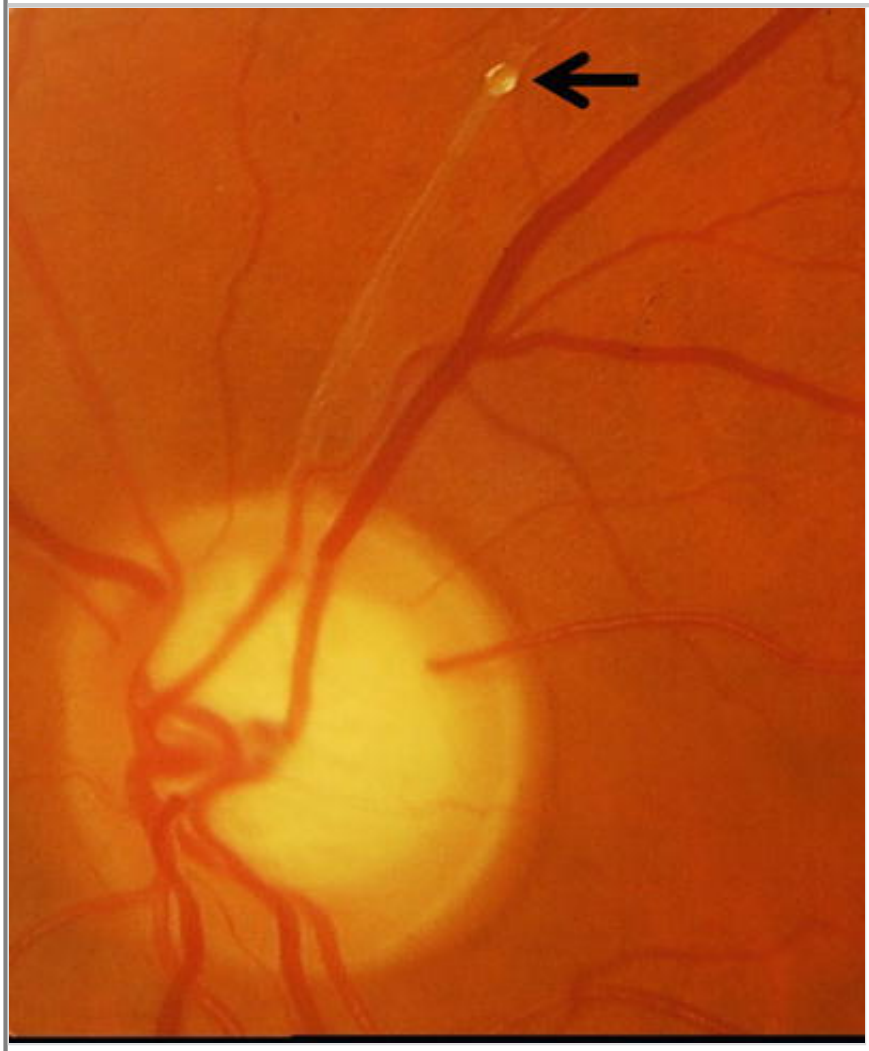
Transcranial Doppler (TCD) ultrasonography can be used to detect microemboli in the cerebral circulation. Microemboli appear as high-intensity transient signals superimposed on the background of standard spectral Doppler flow velocity tracings of red blood cells within the cerebral circulation. TCD has been employed intraoperatively to reveal a large number of microemboli showered into the cerebral circulation during both carotid and coronary artery manipulation. A limitation of this modality is its inability to distinguish atheroemboli from other microemboli including gas, fat, or calcium [50, 51].

The clinical consequence of these microemboli are negligible as a vast majority of patients will demonstrate some evidence of intraoperative cerebral microemboli on TCD, but only a very few patients will manifest postoperative neurological symptoms [52]. Even when new brain lesions suggestive of microembolization are visualized on MRI postoperatively, only a small percentage of patients have clinical findings of transient ischemic attack (TIA) or stroke [53].

Cholesterol emboli originating from atherosclerotic plaque in the ascending aorta, aortic arch, and carotid arteries can cause retinal artery occlusion. Amaurosis fugax is the typical clinical manifestation when there is retinal artery involvement. Retinal exam will often reveal pathognomonic Hollenhorst plaques, which are described as bright, orange-colored plaques seen at the bifurcation of the retinal arterioles (Fig. 27.6) [8].

Fig. 27.6

Hollenhorst retinal plaque. Fundoscopic exam reveals characteristic Hollenhorst plaque (*arrow*) in a retinal artery branch (Courtesy of Dr Irene Cherfas Tsyvine, Department of Ophthalmology, New Jersey Medical School, Newark, NJ)



Kidney

Atheroembolic renal disease should be considered in the differential diagnosis of unexplained acute renal insufficiency (ARI) among older adults. Histologically, atheroembolic renal disease affects predominantly the arcuate and interlobar renal arteries. Rarely, there can be involvement of the afferent arterioles and glomeruli. Renal biopsy is the gold standard for diagnosis but may not always be diagnostic given the patchy nature of disease [54]. Incidence of renal CES can be as high as 7 % among patients aged 60 years or older undergoing renal biopsy for ARI of unknown etiology [55].

In patients with histologically confirmed CES from any other tissue, renal involvement is frequent and can be found in up to 50 % of cases. Proteinuria and elevations in serum creatinine and blood urea nitrogen are the predominant manifestations, occurring in 54 %, 83 %, and 91 %, respectively [56]. Accelerated and difficult to control hypertension has also been described in renal CES and is thought to be secondary to the acute inflammatory response within the renal circulation [57].

Atheroembolic renal disease can result in acute, subacute, or chronic renal insufficiency. Subacute renal insufficiency can be precipitated by manipulation of the aorta during a vascular procedure. In contrast, chronic renal insufficiency is thought to develop from a spontaneous slow release of cholesterol emboli from advanced atherosclerotic plaque in the aorta over an extended period of time [1].

Renal impairment secondary to cholesterol embolization can resolve spontaneously or progress to end-stage disease often requiring renal replacement therapy. Progression to end-stage renal disease is frequent; in an observational study of 354 patients with renal atheroembolism inferred from either renal biopsy or concomitant retinal Hollenhorst plaques, more than 30 % of patients required hemodialysis by the end of a 2-year follow-up. In addition to poor renal recovery, atheroembolic renal disease has also been associated with decreased survival. The 1-year and 2-year survival rates have been reported as 83 % and 75 % respectively, which are lower than those than in other forms of renal disease requiring maintenance hemodialysis [58].

Gastrointestinal Tract

The gastrointestinal (GI) tract is another organ system that is commonly affected by cholesterol embolization. The prevalence of gastrointestinal involvement has been reported anywhere from 18.6 to 48 % of confirmed CES cases [59]. GI atheroembolism often results in abdominal pain and chronic intestinal bleeding secondary to mucosal ulceration and necrosis from bowel wall ischemia. Abdominal CT imaging is nonspecific and may show bowel edema or perforation. Endoscopy has a poor sensitivity, and many of these lesions tend to be microscopic. If endoscopic pathology is visualized, the findings are relatively nonspecific and may demonstrate congested mucosa, mucosal ulcerations or erosions, or focal areas of bluish or necrotic mucosa [60]. In more severe cases, massive bleeding can develop from pseudopolyp formation or frank bowel infarction with subsequent perforation [61].

In addition to bowel, atheroembolism has also been reported to affect other GI organs including the pancreas and gallbladder. Pancreatic involvement can be an uncommon cause of acute pancreatitis in elderly patients [62]. Cholesterol embolization can also be a rare etiology of acalculous cholecystitis, especially following a recent vascular procedure [60].

Skin

The incidence of cutaneous manifestations in cholesterol embolization syndrome ranges from 35 to 96 % [63]. In one of the more comprehensive dermatologic case series of patients with confirmed CES, cutaneous findings were seen in 35 % of cases (78 of 223 patients). The most common skin manifestations are livedo reticularis (49 %), gangrene (35 %), cyanosis (28 %), ulceration (17 %), nodules (10 %), and purpura (9 %). Skin findings are located predominantly on the lower extremities; they are much less common on the trunk or upper extremities [64]. Cutaneous biopsies are reasonably sensitive for the diagnosis of CES and are positive in approximately 92 % of patients with skin manifestations [63].

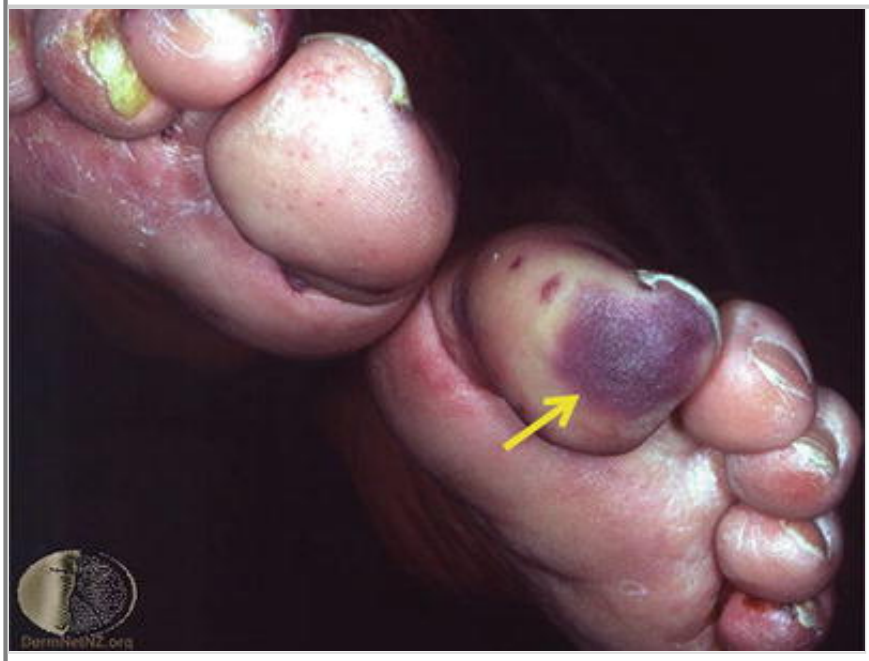
Livedo reticularis appears as a rash of reddish blue spots distributed in a fishnet or lacy pattern. This finding represents a cyanotic response caused by restriction of blood flow due to narrowed arterioles within the skin. Although a common clinical finding that should raise suspicion for CES, especially in an elderly patient, livedo reticularis is not pathognomonic for atheroemboli and can be seen in other disorders that are associated with skin ischemia including polyarteritis nodosa, systemic lupus erythematous, cryoglobulinemia, and treatment with vasoconstrictive agents [63].

In the lower extremities, cholesterol crystal emboli can lead to the sudden development of blue or purple

toes (Fig. 27.7) [13]. This finding was first described in 1976 by Karmody as a manifestation of CES [9]. Because the sudden development of blue toes has a significant association with atheroembolism, the term blue toe syndrome is sometimes used clinically as a synonym for CES.

Fig. 27.7

Blue toes. An *arrow* points to bluish discoloration of the left big toe, a manifestation of microvascular ischemia in a patient with cholesterol embolization syndrome (Courtesy of Dr. Amanda Oakley, New Zealand Dermatological Society Incorporated; image reprinted with permission from DermNetNZ.org)



Development of blue toes represents microvascular ischemia, and although frequently seen in atheroembolic disease, it is a nonspecific finding than can also be seen in other conditions including vasculitis (polyarteritis nodosa), hypercoagulable states (antiphospholipid syndrome), hyperviscosity states (polycythemia vera), and endocarditis [65]. Toe and foot cyanosis in blue toe syndrome is more prevalent in dependent areas, typically blanches with moderate pressure, and is often asymmetric when both lower extremities are involved. If microvascular ischemia is severe, a spectrum of tissue necrosis can be seen ranging from superficial ulceration to gangrene (decay of dead tissue due to lack of a blood supply) [1].

Generally, when cutaneous manifestations are seen, they often occur in the context of palpable distal pulses because cholesterol crystal emboli are more likely to affect the smaller arteries and arterioles than the larger palpable arteries. Therefore, palpable distal pulses in the lower extremities may favor the diagnosis of CES over other forms of peripheral vascular disease. However, patients with atheroembolism often have other manifestations of advanced atherosclerotic disease including peripheral arterial disease that can independently cause diminished palpable pulses. Thus, absence of palpable pulses does not exclude CES [1]. Patients with blue toe syndrome secondary to CES are more likely to have other cutaneous manifestations including livedo reticularis.

Diagnosis of Cholesterol Emboli Syndrome

Diagnosis of CES is a challenge given that there is no definitive laboratory test or pathognomonic

clinical presentation. The syndrome can affect any organ system and can present as a slow insidious process with nonspecific signs and symptoms mimicking a vast array of systemic illnesses. The cornerstone of diagnosis is predominantly clinical and based on the combination of signs and symptoms of end-organ damage in a patient with a recent history of an intra-arterial procedure and/or risk factors for advanced atherosclerosis (male, advanced age, hypertension, diabetes mellitus, hypercholesterolemia, and a history of tobacco use) [1].

Secondary to the provoked inflammatory response described above, patients can exhibit constitutional symptoms such as fever, weight loss, anorexia, fatigue, and generalized myalgia. There can also be an array of laboratory abnormalities; however, they are typically suggestive of rather than diagnostic of CES. Elevation of inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is common and can be associated with a reactive leukocytosis. Hypocomplementemia has also been reported. Patients can have evidence of a normocytic anemia and thrombocytopenia. When there is renal involvement, the serum creatinine and blood urea nitrogen are often elevated, and proteinuria may be present.

Hypereosinophilia may also be a marker of CES. It has been reported in up to 80 % of CES cases, although the duration and degree of hypereosinophilia can be variable. One study found that the prevalence of eosinophilia ranged from 6 to 18 % of the total leukocyte count and persisted only for the first several days of the initial event [66]. The mechanism for hypereosinophilia in atheroembolism remains unknown. It is hypothesized to be cytokine mediated and may be related to release of interleukin-5 derived from vascular endothelium [67]. Similar to other laboratory findings, hypereosinophilia is not pathognomonic for CES. When associated with acute or progressive renal insufficiency, the differential diagnosis of hypereosinophilia includes systemic vasculitis, acute interstitial nephritis (AIN), and radiographic contrast-induced nephropathy (CIN) [66].

Given that the clinical and laboratory findings described thus far are not specific for the diagnosis of CES, it must be emphasized that a high degree of clinical suspicion is required in order to establish the diagnosis. If patient characteristics, clinical history, and laboratory findings are suggestive of atheroembolism, then an ophthalmologic exam demonstrating Hollenhorst plaques and/or aortic imaging revealing complex atherosclerotic plaques may further support the diagnosis, especially in the absence of a recent vascular procedure when spontaneous plaque rupture may be the underlying etiology.

Ultimately, pathological confirmation from a biopsy specimen remains the only definitive test for CES [68]. Technically any affected tissue can be targeted for biopsy, but the skin and skeletal muscle are the preferred sites secondary to the ease of the procedure and reduced patient discomfort. Cutaneous biopsies have a sensitivity of 92 % per one review [63]. Despite the utility of a biopsy in confirming the diagnosis of cholesterol embolization, biopsy is performed infrequently due to the concern that the biopsy sites may heal poorly given that these tissues are located in regions of restricted blood flow.

Treatment of Cholesterol Emboli Syndrome

At this time, no specific therapy is available for CES [69]. Management of atheroembolic disease focuses on supportive care for end-organ damage sustained and prevention of future cholesterol embolic events. In addition, measures should be taken to aggressively manage atherosclerotic disease risk factors including blood pressure control, lipid management, adequate glucose control, and smoking cessation.

Although no randomized trial data is available, there is some data to support the use of statin therapy. One retrospective study that included 519 patients with severe atherosclerosis visualized on TEE found that statin use was independently associated with a reduced incidence of future embolic events [29].

Another study that included 354 patients diagnosed with atherosclerotic renal disease reported a 50 % reduction in the need for renal replacement therapy or mortality among patients on statin therapy [58]. Future randomized trials may provide more evidence base for statin use in atheroembolic disease [70].

Antiplatelet therapy has been considered for the management of cholesterol embolization. However, there is no direct evidence that their use reduces recurrence of embolic events. Regardless, antiplatelet therapy is reasonable in CES considering that there is strong evidence to support that they reduce adverse cardiovascular events including myocardial infarction which is the leading cause of death among patients with atherosclerotic disease [71]. Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers (ARB) are also reasonable to consider especially in patients with hypertension, diabetes, and/or renal involvement [72 , 73]. There is limited data on the use of corticosteroids which may mitigate the inflammatory response in atheroembolic renal disease with a suggestion of favorable short-term outcomes. However, loss of benefit was seen in more long-term follow-up [74 , 75].

As previously noted, the routine use of thrombolytic or anticoagulation therapy is not recommended given the uncertainty of their involvement in precipitating plaque rupture. Specifically, anticoagulation therapy should not be initiated in CES unless there are other established indications such as atrial fibrillation, left ventricular thrombus, deep venous thrombosis, or a mechanical prosthetic valve [1].

In patients with prior episode of CES, when considering future intra-arterial diagnostic or therapeutic interventions that involve the aorto-iliac-femoral system including angiography, percutaneous coronary revascularization, and cardiovascular surgery, risk of recurrent CES should be weighted carefully against benefits. Generally, elective intra-arterial procedures should be avoided.

Surgical or endovascular procedures may be a treatment option in patients with CES. They may be considered when a clear source of cholesterol emboli can be identified, the site is surgically or endovascularly accessible, and the patient is an appropriate surgical candidate. Such management is aimed at the surgical removal or endovascular exclusion of advanced atherosclerotic plaque felt to be the culprit. The data has shown this strategy to be effective in reducing the rate of future embolic events in appropriately selected patients [76 , 77].

Conclusion

CES is a rare disease process with a high incidence of morbidity and mortality. The syndrome results from microembolization of plaque debris, including cholesterol crystals, from rupture of complicated atherosclerotic plaques found within large, proximal arteries usually in the aorta-iliac-femoral system. Plaque rupture can be spontaneous or as a result of aorta-iliac-femoral manipulation during intravascular catheter-based procedures or cardiovascular surgery. These microemboli become lodged within small caliber distal arteries and arterioles leading to mechanical obstruction and inflammation resulting in end-organ damage. Potentially, any organ can be affected resulting in variable clinical manifestations ranging from encephalopathy, gastrointestinal bleeding, renal insufficiency, and livedo reticularis to “blue toes.” Constitutional symptoms such as fever, weight loss, and fatigue can also occur as a result of the acute inflammatory response. Nonspecific laboratory findings arising from this inflammatory response may include an elevated ESR, leukocytosis, and hypereosinophilia. Pathological diagnosis, obtained from biopsy of affected tissue, continues to be the gold standard for diagnosis. Treatment remains largely supportive.

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