Review Article

Cholesterol crystal embolization following plaque rupture: a systemic disease with unusual features

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Abstract

Cholesterol crystal embolic (CCE) syndrome is often a clinically challenging condition that has a poor prognostic implication. It is a result of plaque rupture with release of cholesterol crystals into the circulation that embolize into various tissue organs. Plaque rupture seems to be triggered by an expanding necrotic core during cholesterol crystallization forming sharp tipped crystals that perforate and tear the fibrous cap. Embolizing cholesterol crystals then initiate both local and systemic inflammation that eventually lead to vascular fibrosis and obstruction causing symptoms that can mimic other vasculitic conditions. In fact, animal studies have demonstrated that cholesterol crystals can trigger an inflammatory response *via* NLRP3 inflammasome similar to that seen with gout. The diagnosis of CCE syndrome often requires a high suspicion of the condition. Serum inflammation biomarkers including elevated sedimentation rate, abnormal renal function tests and eosinophilia are useful but non-specific. Common target organ involvement includes the skin, kidney, and brain. Various testing including fundoscopic eye examination and other non-invasive procedures such as trans-esophageal echocardiography and magnetic resonance imaging may be helpful in identifying the embolic source. Treatment includes aspirin and clopidogrel, high dose statin and possibly steroids. In rare cases, mechanical intervention using covered stents may help isolate the ruptured plaque. Anticoagulation with warfarin is not recommended and might even be harmful. Overall, CCE syndrome is usually a harbinger of extensive and unstable atherosclerotic disease that is often associated with acute cardiovascular events.

Keywords: cholesterol crystal embolic syndrome

Introduction

Cholesterol crystal embolism (CCE) refers to the embolization of cholesterol crystals (CCs) released from atherosclerotic plaques lining the walls of the aorta or major inflow arteries that showered particulates downstream *via* smaller arteries and arterioles to end organs. This leads to a variety of clinical manifestations that

depend on the specific organ affected by emboli as well as systemic symptoms[1]. Cholesterol crystal embolization is an under-recognized disease that can occur spontaneously or accompany a myriad of vascular and endovascular procedures[2]. The first single autopsy findings was described in 1862 by the Danish pathophysiologist Peter Ludvig Panum[3]. Eighty years elapsed before the first autopsy series by Curtis Flory who provided support to the theory of distal embolization of CCs from eroded aortic plaques as a cause of arterial occlusions rather that the theory of *in situ* formation of CCs[4]. The most commonly involved organs are the skin and the kidneys with a plethora of nonspecific signs and symptoms that include fever, weight loss, myalgias and headache[1-2]. This can result in presentations mimicking various other diseases (i.e. polymyositis) leading to difficulties and delays in diagnosis, thus making this CCE a "great masquerader".

Epidemiology

CCE has been noted to predominantly affect males (age over 60 years) often with clinical evidence of atherosclerotic cardiovascular disease[1-2,4-5]. The true incidence of CCE varies widely due to inconsistency in diagnostic approaches based on the reporting used i.e. clinical (mainly dermal manifestations or elevation in serum creatinine) or histopathological criteria by biopsy.

In retrospective analysis, the incidence of postmortem spontaneous CCE has ranged between 0.79% and 3.4% in unselected series of autopsies of patients over 60 years[2,4,6]. The overall prevalence of CCE following cardiac catheterization has been reported in autopsy studies to be as high as 25%-30%[7]. In one retrospective study of patients with severe thoracic aortic plaque seen on transesophageal echocardiogram (TEE), the incidence of spontaneous antemortem clinical CCE was about 1%[8]. However, clinical, angiographic and pathologic CCE were found in about 2.9% of patients undergoing infrarenal aortic and infrainguinal vascular surgery[9] and 1.6% following aortoiliac stent placement[10]. Patients who underwent myocardial revascularization or valve operations and had evidence of severe atherosclerosis of the ascending aorta were found to have an increased incidence of CCE with 21.7% in the autopsy series[11].

Prospectively, the occurrence of clinical CCE was found to be around 1.4% in patients undergoing left heart catheterization. Surprisingly, no significant difference in the risk of CCE was noted between the brachial and femoral approach implicating the ascending thoracic aorta as a main embolic source[12]. The

incidence of pathologic CCE may be higher due to high rate of aortic debris retrieved with placement of guiding catheters during percutaneous interventions. This, however, did not seem to result in greater in-hospital ischemic events[13].

Among patients undergoing coronary artery bypass grafting (CABG) within 1 month of an acute myocardial infarction, muscle and skin biopsies done at the site of vein harvest demonstrated a 12% incidence of CCE. There was no significant difference between those who received thrombolytic therapy and those who did not; most of the cases were subclinical[14]. Overall, retrospective autopsy or biopsy studies may detect subclinical disease and thus exaggerate the frequency of CCE; whereas the incidence of CCE in clinical reports is considerably less and can be affected by sample characteristics and the duration of follow up. In addition, the inherent selection bias of autopsy studies may explain the discrepancy between pathology and clinical data. The incidence of CCE may be expected to increase with a rise in the aging population and the number of vascular procedures performed. The current estimates of incidence are probably greatly underestimated because tissue preparation methods using ethanol dehydration dissolves CCs[15]. This could greatly skew the data in favor of a lower incidence of CCE when using standard histological methods.

Clinical predisposing factors to embolization

Cholesterol crystal embolization can occur either spontaneously or as a complication of mechanical trauma during aortic surgery, angioplasty and various angiographic procedures such as aortography, left heart catheterization and peripheral angiography[2,9-10,12]. Several predisposing factors have been associated with the development of CCE following cardiac and endovascular procedures. These include hypertension, heavy smoking, hypercholesterolemia, diabetes mellitus, renal failure, advanced age, peripheral vascular disease and severe atherosclerosis of the ascending aorta[1,10-11]. Although white race has been implicated as a risk factor, CCE is likely underdiagnosed among blacks[1,16].

Sporadic case reports have hypothesized a causal relationship between CCE and thrombolytic administration for myocardial infarction or deep venous thrombosis[14]. The use of thrombolytic or anticoagulant treatment may facilitate CCE possibly by preventing thrombus formation over ulcerated plaques, promoting plaque hemorrhage or interfering with the stabilization of CCs within atheromatous plaques by platelet-fibrin thrombi. Several large trials of thrombolytic therapy

have not reported CCE and the association between thrombolytic administration and CCE is probably weak and the occurrence is difficult to predict[1-2,14]. Although some claim that anticoagulation can worsen CCE clinical condition[17], one study using warfarin compared to no warfarin did not appear to alter the rate of CCE in patients with severe atherosclerotic plaque of the thoracic aorta visualized by TEE[8]. Use of emerging risk markers such as elevated C-reactive protein (CRP) levels and higher resolution imaging techniques may help in detecting the presence of inflamed and unstable plaques that are associated with an increased risk for CCE[12,18].

Pathogenesis

Cholesterol crystal formation is favored by several intra- and extra-cellular factors. Intracellular factors include the enhanced activity of cholesterol ester hydrolase enzyme or reduction in the Acyl-CoA: cholesterol acyltransferase (ACAT). Also, reduced HDL and/or dysfunctional HDL contributes to this process (*Fig. 1*)[19]. Local extracellular factors include a mild drop in local temperature, increased saturation of cholesterol, hydration of the cholesterol molecule and an alkaline milieu[20]. The formation of CCs is associated with an inflammatory response both locally and systemically[21-22]. Crystals form early in the atherosclerotic process and activate the inflammasome NLRP3 leading to the secretion of IL-1β[22]. This triggers a systemic response with IL-6. The process is similar to how monosodium urate crystals trigger inflammation in gout[23]. Overall, inflammation leads to arterial wall remodeling and destabilization of atherosclerotic plaques making them more prone to rupture.

The correlation between CCE and aortic atherosclerosis was first suggested by Flory in 1945[4] and was readdressed over 30 years later by Kealy who demonstrated that in every case of peripheral embolism the aorta had advanced plaques, sometimes with aneurysm formation[6]. Unstable plaques that are vulnerable to rupture have been defined histologically to have a lipid-rich necrotic core, a thin fibrous cap, reduced structural support and presence of cellular inflammation that can weaken the fibrous cap[24]. However, it is cholesterol crystallization within the plaque's necrotic core that leads to volume expansion that can rupture the fibrous cap. Perforation of the intimal surface by growing sharp tipped CCs may also cause erosion and trigger thrombosis[25,26]. Autopsy findings demonstrate that only patients who died of acute myocardial infarction had CCs perforating the intima while those who died of other causes and had significant arterial plaques did not
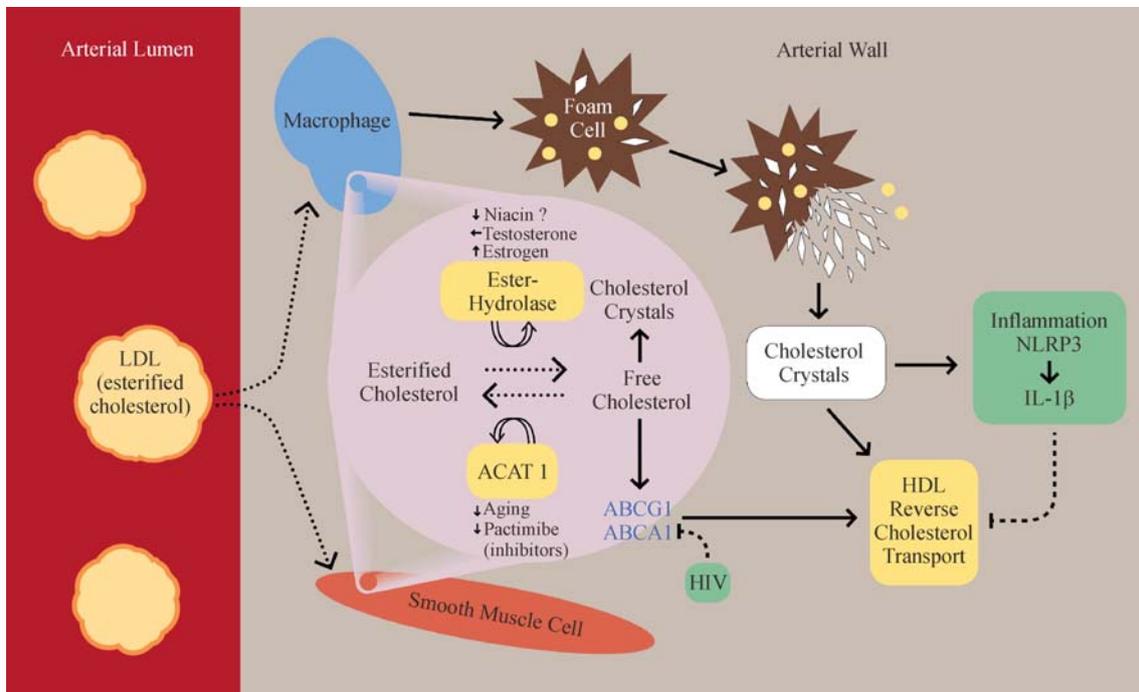

Fig. 1 **Cholesterol transport within cells and extracellular space.** Equilibrium between esterified and free cholesterol is noted with membrane transporters driving free cholesterol into the extracellular space where it is taken up by high-density lipoprotein. Dying foam cells overloaded with esterified cholesterol and crystals release their content into the extracellular space. Free cholesterol build-up in the extracellular space leads to crystallization. ABCA1, ABCG1, ATP binding cassette A-1, G-1; ACAT 1, acyl-coenzyme A cholesterol acyltransferase 1; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IL-1β, interleukin-1β; LDL, low-density lipoprotein; NLRP3, NLRP3 inflammasome. Reproduced with permission[19].

have CCs perforating the intima[27]. In an atherosclerotic rabbit model, those with a greater plaque burden had more CCs, serum inflammation, macrophage infiltration and thrombosis[21]. Also, in the rabbit model, light and scanning electron microscopy demonstrated CCs in the inflamed fibrous cap and perforating the intima at the sites of plaque rupture[21,28]. Moreover, CCs can readily puncture the vasa vasorum within the plaque causing intra-plaque hemorrhage that can contribute to plaque rupture[25,27]. Also, iatrogenic causes such as catheter manipulation during intra-arterial procedures or the increase in local shear stress with elevated blood pressure can be other factors contributing to plaque disruption[12,29].

The aorta and iliac arteries are the most common source of particulates that cause embolization followed by the femoral arteries, while the popliteal and subclavian arteries are rarely involved which may explain the rarity of upper extremity involvement in CCE[30]. One of the more critical sources for embolization is the carotid arteries (**Fig. 2**). These emboli often travel to the cerebral and retinal micro- and macro-circulation causing cerebral inflammation and/or transient ischemic events as well as strokes. Denudation or rupture of plaques allows their underlying extracellular cholesterol-rich matrix free access to disseminate into the arterial bloodstream[1]. These microemboli of CCs measure about 50 to 200 μm and can lodge into distal
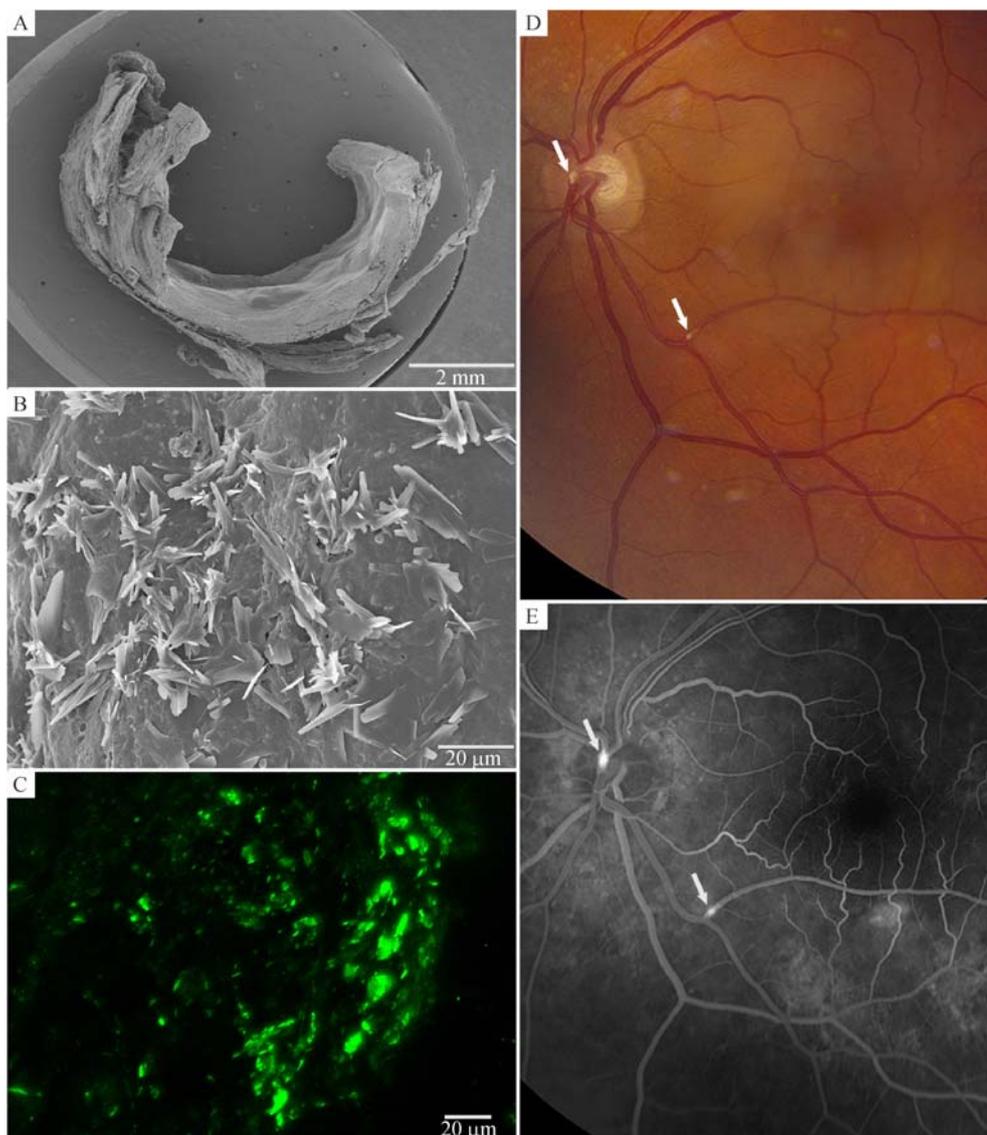

Fig. 2 **Imagings of cholesterol crystals.** A: Low power scanning electron micrograph of carotid artery plaque. B: Surface scanning of the plaque demonstrates extensive cholesterol crystals. C: Fluorescence image of cholesterol crystals on the intimal surface of the artery using Bodipy stain for cholesterol crystals (Courtesy of Dr. G. Abela). D and E: Fundoscopyof Hollenhorst plaques of embolized cholesterol crystals in retinal arteries (arrows, Modified from Elizabeth Gauger, MD and Toni Venckus, CRA, University of Iowa; http://webeye.ophth.uiowa.edu/eyeforum/atlas/pages/Hollenhorst-plaque.htm).

capillaries, arterioles and small arteries. This can also lead to narrowing or obliteration of small arterial lumens resulting in ischemia or infarction[16].

In addition to mechanical injury, CCE can create inflammatory and endothelial vascular reactions. These changes were reproduced by intravenous injection of CCs in the ear veins of rabbits and performing histologic examination of the lungs at various intervals[4,31]. In these models, an early panarteritis (24-72 h) was demonstrated with mononuclear and eosinophilic cell infiltration in addition to giant cells adjacent to CCs and adventitial leukocytes. Later (2-7 days), endothelial proliferation with intravascular fibrosis occurs and CCs are engulfed by giant cells[1,31]. The later changes have been found to persist to the last interval examination at 160 days[31]. Other pathologic changes may occur and include formation of intravascular thrombosis (24-72 h), and the penetration of the vascular endothelium by crystals with secondary adventitial fibrosis (days to months)[1]. The end product of CC embolism are inflammation and injury with eventual fibrosis and obliteration of the arterial lumen[17,31].

Although it has been known that CCs could be found in or attached to the surface of the intima creating local inflammation[4], we also demonstrated that CCs can damage the endothelium and reduce its vasodilator response (*Fig. 3*)[32]. Moreover, this effect was due to the scraping of the intimal surface of the artery by sharp CCs traveling downstream. Intravascular CCs were thought to be insoluble and resist the scavenger effects of the macrophages[1,31].

Histopathology

Cholesterol crystal embolization can be defined by histopathology as the presence of the typical lesions found in arterial lumens as first described by Flory in 1945[4]. The arterial lumen is filled with large CCs spaces (dissolved during the preparation) surrounded by hyperplastic intimal tissue and giant cells. Cholesterol emboli of various ages can be found suggesting that the process of embolism is recurrent[2]. The external diameter of the arteries plugged with cholesterol emboli vary from 150 μm to 1100 μm in diameter[13]. Since CCs are readily dissolved when using standard methods with ethanol dehydration for preparing histologic sections, the amount of CCs has been greatly underestimated by light microscopy[15,25,27]. However, by using vacuum dehydration in tissue preparation for scanning electron microscopy or just fresh tissue with fluorescence microscopy, Abela *et al.* were able to demonstrate the vast extent and effect on tissue injury by CCs[15,25–27,33]. This demonstrates CCs

perforating the fibrous cap in atherosclerotic plaques and extensive amount of CCs released into the circulation. Also, in an early study Eliot et al. recognized this problem and attempted to use polarized light on frozen preparations to detect CCs[31].

Clinical Presentation

Although any site of the body can be affected by CCE, the aorta and iliac arteries are the most commonly recognized sources of embolization followed the femoral arteries (the popliteal and subclavian arteries are rarely involved) which explain the rarity of upper extremity involvement in CCE[30]. However, the carotids are another common source of crystal embolization to the brain causing neurological symptoms (*Fig. 2*)[6,30].

Constitutional symptoms

The presenting symptoms and signs of disseminated CCE are often nonspecific and range from subtle to catastrophic. Disseminated CCE may produce constitutional and systemic symptoms that include fever, weight loss, fatigue, myalgia and anemia of chronic disease[1]. Skin and the kidneys are the most common organs affected by CCE and their manifestations are often used as clinical diagnostic criteria for CCE. Histology is consistent with a pseudovasculitis with giant cell reaction (*Fig. 4*).

The following is a brief review of the most frequent end-organs involved and their clinical presentations.

Skin: Cutaneous manifestations are the most common finding in CCE patients with frequency ranging between 35% and 96%[16-17]. Livedo reticularis is the most common skin manifestation followed by gangrene, cyanosis, ulceration and less frequently nodules and purpura[1,16]. The lower extremities are most commonly involved, and except for gangrene and ulcerations the cutaneous lesions associated with CCE are generally bilateral[16].

Livedo reticularis is a red-blue discoloration of the skin distributed in a net-like arrangement that represents a cyanotic response pattern commonly associated with intravascular obstruction of small vessels[34]. It occurs suddenly in cases of CCE and is quite extensive extending from the feet to the buttocks and trunk.When it occurs in the elderly, it implies the presence of CCE[16]. Other causes of livedo reticularis include coagulopathies like cryoglobulinemia and vasculitic syndromes like polyarteritis nodosa[34].

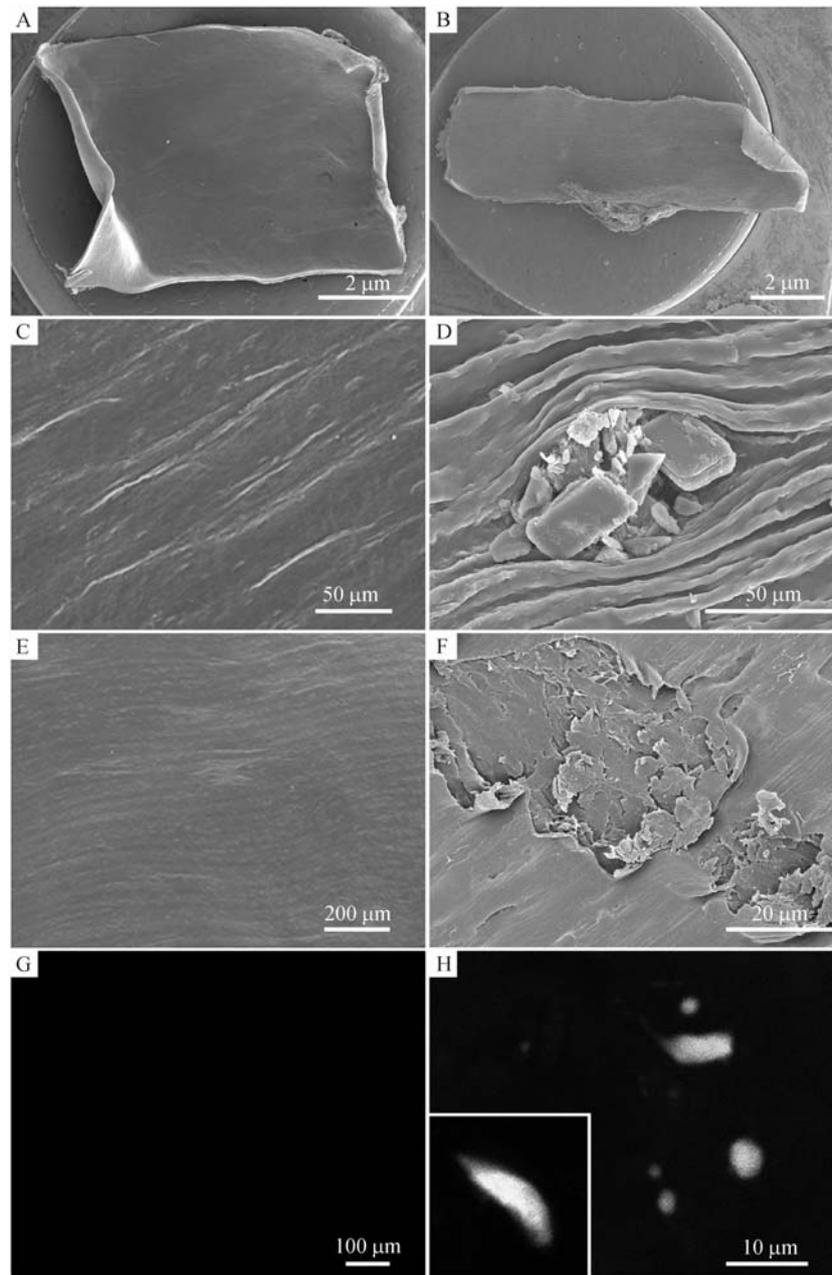Toe involvement is manifested by blue or purple discoloration that has traditionally been considered the

***Fig. 3* Microscopic images with scanning electron microscopy and confocal microscopy of arterial surface injury.** A-F: scanning electron microscopy; G-H: confocal microscopy. Circulating saline control (A, C, E, and G) vs. circulating cholesterol crystals (B, D, F, and H). No intimal injury is present with control arteries but extensive injury is present with cholesterol crystals. Cholesterol crystals are seen embedded and disrupting the intimal surface of the artery (D, F, H) with circulating cholesterol crystals. Modified and reproduced with permission[31].

sine qua non for diagnosis. The etiology is probably microvascular ischemia which can be seen as well in coagulopathies and vasculitides[16].

Kidney: Renal involvement is the second most common manifestation of CCE due to proximity of the kidneys to the abdominal aorta and their large blood supply, and could be found in up to 50% histologically proven CCE[1]. The presentation can range from subclinical illness to fulminant disease although it is mostly subacute arising within 1 week of an CCE event with progressive worsening of renal function[1,17,30].

Eosinophilia is commonly seen with renal CCE (in up to 80% of patients) but is transient, lasting only a few days[30]. The urine sediment is usually benign (with few cells and a minimum amount of proteinuria) which helps differentiate renal CCE from systemic vasculitis[5,17]. Less common presentation is a chronic, slowly progressive renal impairment with absence of extrarenal signs. The chronic course is commonly attributed to hypertensive nephrosclerosis or ischemic nephropathy, which frequently co-exists with cholesterol emboli. This often clinically silent crystal showering, frequently goes

Fig. 4 **Histology of cholesterol crystals consistent with a pseudovasculitis with giant cell reaction.** A: Intraglomerular renal cholesterol crystals; B: cholesterol crystals in an arcuate artery with encasement of a crystal by a giant cell and pseudovasculitis inflammatory reaction (arrow); C: purpuric lesion over knees; D: skin biopsy with cholesterol crystals; blue toe (E) embolic crystals (F) in skin arterioles. Modified and reproduced with permission [17].

underdiagnosed because extrarenal signs are absent and renal biopsy samples are not taken[17]. Infrequently, patients may have accelerated hypertension but rarely a renal infarction[1,17]. One cannot exclude the possibility of contrast nephrotoxicity as a contributor to post-procedural nephropathy. A useful approach is to consider the creatinine increase within several days to be due to contrast nephrotoxicity and that at 1-2 weeks to suggest CCE[12].

Renal atheroembolic disease follows a variable course. Renal replacement therapy is needed in about 28%–61% of patients with acute or subacute disease, with partial recovery expected in 20%–30%. This is probably due to resolution of inflammation or reversal of concurrent ischemic acute tubular necrosis[5,17].

Gastrointestinal System: The frequency of gastro-intestinal (GI) findings among CCE patients ranges from 10 to 36%[5,35]. Two patterns of disease can be identified: acute catastrophic multiorgan presentation and chronic and more indolent GI disease. The most common manifestations are abdominal pain, diarrhea, and GI blood loss resulting from bowel ischemia, mucosal ulcerations, hepatocellular liver disorder, and/or pancreatitis[31,35]. Cholecystitis gall bladder involve-ment, although rare, tends to be clinically significant especially in the elderly, with a spectrum ranging from chronic acalculous cholecystitis to acute, necrotizing and ischemic disease[35].

Coronary Arteries: Embolization of CCs within the coronary arterial circulation has not been extensively

investigated[36]. However, a few case reports demonstrate that CC emboli into the coronary arteries have been associated with sudden cardiac death[17]. Debris released during plaque rupture within the coronary arteries includes not only CCs but also platelets, cell debris, fibrin and red blood cells. CCs and platelets are some of the various ejected materials that can trigger an inflammatory response. In fact during myocardial infarction, the arterial lumen could be occluded entirely by CCs released during plaque rupture[26]. However, the great amount of CCs present in coronary lumen following plaque rupture has been greatly underestimated due to the standard tissue processing methods with ethanol that dissolves CCs (*Fig. 5*)[15,37].

Central Nervous System: Central nervous system manifestations can range from transient ischemic attack and acute stroke to a gradual deterioration of neurological function and dementia[38-39].

Release of CCs into the cerebral circulation breaks down the blood brain barrier and initiates an inflammatory response without evidence of ischemia[40]. This can result in loss of memory and other integrative cerebral functions.

Brain imaging reveals mostly multiple, small ischemic lesions and border zone infarcts[39]. Retinal involvement can be occasionally demonstrated by Hollenhorst plaques which are bright, refractile lesions indicative of CCE. They can occur in asymptomatic patients but are a poor predictor of future embolic events[41].

Other vascular beds including coronary, pulmonary, testes, prostate, thyroid and adrenal glands are rarely manifested clinically and their involvement is confirmed by pathology[1].

Diagnosis

Cholesterol crystal embolization becomes evident when showers of cholesterol microemboli cause enough damage to end organs to be detected clinically or by imaging and laboratory methods. Laboratory findings are usually nonspecific and include leukocytosis, thrombocytopenia, anemia and raised concentrations of inflammatory markers (erythrocyte sedimentation rate (ESR) or C-reactive protein)[1,17]. Transient eosinophilia tends to occur more in patients with renal involvement[1,12,17]. In addition, laboratory abnormalities may reflect specific organ injury such as azotemia, hyperamylasemia (due to pancreatic or bowel involvement), elevated creatine kinase due to muscular involvement, and elevated transaminases due to hepatic injury[1]. In cases where hypocomplementemia is present, there is a need to rule out embolic disease from bacterial endocarditis[5]. Occasionally, antemortem histological examination may be necessary for definite diagnosis; biopsies have mostly come from skin, muscle or kidney with a few *via* other tissue types like the colon[1,5,33,35].

Fundoscopic eye examination may be the easiest and most reliable method to evaluate if there is CCs showering and is often associated with other sites of embolic events[17]. Other noninvasive imaging modalities such as TEE, computed tomography (CT) and magnetic resonance imaging (MRI) have gained an increasing role in confirming the diagnosis of CCE. TEE has become the standard test in diagnosing thoracic aortic disease due to its portability and lack of ionizing radiation or need for contrast agents. TEE can diagnose the higher risk complex plaques defined by their protuberance ($\geqslant 4$ mm), ulceration or the presence of mobile components (*Fig. 6*)[8,42]. Non-calcified plaques may be more lipid-laden and probably associated with higher embolization risk[8]. Transcranial Doppler (TCD) has been shown to detect particulates ejected from ruptured carotid plaques[43]. Moreover, simultaneous TCD and carotid ultrasound may provide additional insights into potentially unstable plaques[32].
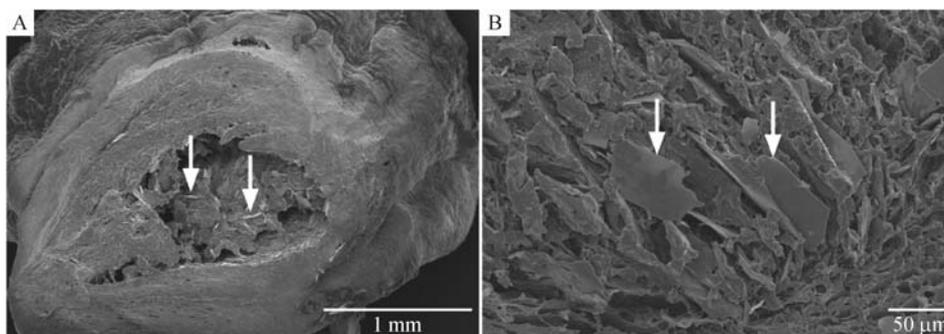
Both CT and MRI offer a more complete evaluation

***Fig. 5* Scanning electron micrograph of coronary artery from patient who died during an acute myocardial infarction.** A and B: Circumflex artery is totally occluded with thrombus loaded with cholesterol crystals (arrows). Crystals are evident when ethanol is not used in the tissue preparation. Modified and reproduced with permission [19].
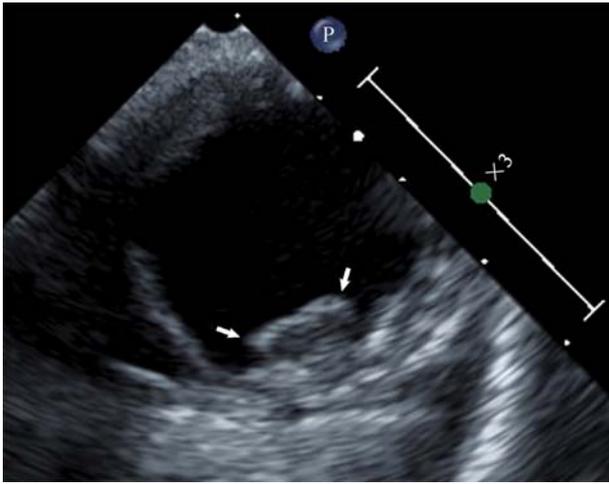
Fig. 6 **Transesophageal ultrasound of the ascending aorta from an asymptomatic patient examined for mitral regurgitation.** Ulcerated plaque is visibly lining the aorta with overlying thrombus (arrows) (Courtesy Dr. N. Thormeire).

of the aorta and the chance to image other potential arterial source[44]. Nonenhanced CT can assess for both calcium deposits and areas of hypoattenuation adjacent to aortic wall and the same 4 mm thickness for protruding plaque can be used to identify high risk patients. It is recommended though, that any positive nonenhanced CT study be followed with a confirmatory contrast-enhanced CT or TEE[45]. Gadolinium-enhanced 3D MRA is also a useful modality to visualize plaques in contiguous ascending aorta, which cannot be seen with TEE due to tracheal interposition[44].

Currently conventional catheter angiography is being used less frequently in favor of less invasive imaging techniques. However, if therapeutic endovascular procedures are contemplated, a catheter angiogram is needed as a "road map". Depending on the concentration of iodine used, plaques can be seen as "filling defects" within the contrast-enhanced lumen or inferred from irregularities of the luminal surface[44]. Also intravascular imaging techniques like optical coherence tomography (OCT) have been shown to identify macrophage accumulations and large, extracellular cholesterol crystal plates in the vascular endothelium[46]. Recently, a newer advancement called micro – OCT, which has 10 times higher resolution than conventional OCT, has been shown to image endovascular subcellular structures including individual macrophages and cholesterol crystal within those macrophages[47]. Due to lack of specific clinical presentations or diagnostic tests, a high index of suspicion should remain in patients presenting with livedo reticularis, cyanotic toes and/or subacute renal failure. This becomes especially important in elderly

patients with evidence of atherosclerosis that underwent a recent cardiovascular procedure.

Management

Prognosis of CCE is generally poor with in-hospital mortality ranging between 5 and 16%[12,30,48] and up to 81% in autopsy case series[1]. Treatment is mostly supportive and includes, treating underlying heart failure and hypertension, nutritional support and if needed renal replacement therapy with ultrafiltration and hemodialysis[48]. Despite its weak link to CCE, anticoagulation has been advocated to be stopped or not initiated in patients with CCE[1,17,30,48]. Unfortunately, the highly anticipated ARCH trial that evaluated the efficacy of aspirin plus clopidogrel versus warfarin in patient with aortic arch atherosclerotic plaques >4 mm did not achieve statistical power to demonstrate a difference between either intervention. However, aspirin plus clopidogrel had a lesser primary endpoint of vascular death compared to the warfarin group[49]. Thus, in the absence of clear correlation of antiplatelet therapy to inducing CCE, their use should follow established guidelines.

Animal studies have shown that statins (HMG-CoA reductase inhibitors) can reduce matrix metalloproteinase expression in atheromas and may lead to an increase in fibrous cap thickness in association with collagen accumulation[50]. In humans, established statin therapy can decrease the incidence of plaque rupture as detected by intravascular ultrasound[51]. In a retrospective analysis of patients with severe aortic atherosclerosis seen on TEE, the use of statins was associated with protective effect on atheroembolic recurrence rate, though, no significant benefit of warfarin or antiplatelet drugs was detected[8]. In a prospective observational study of patients with spontaneous CCE, statin treatment was associated with protective effects both when already in place at the time of diagnosis and when initiated after diagnosis[5]. In addition, statins have been shown to reduce CRP[52] and dissolve CC in human plaques (*Fig. 7*) [53]. Anecdotally, simvastatin has been reported to improve renal dysfunction caused by CCE, but further prospective studies are needed to investigate the usefulness of statins after the onset of symptoms. Indirect evidence from acute coronary syndromes suggests that higher doses of statins provide better protection[52,54]. Although older reports have linked the use of steroid to poor prognosis[1], the results of more recent studies with steroid therapy have suggested that low dose might be beneficial[48]. A recent retrospective study of steroid therapy in patients with renal CCE
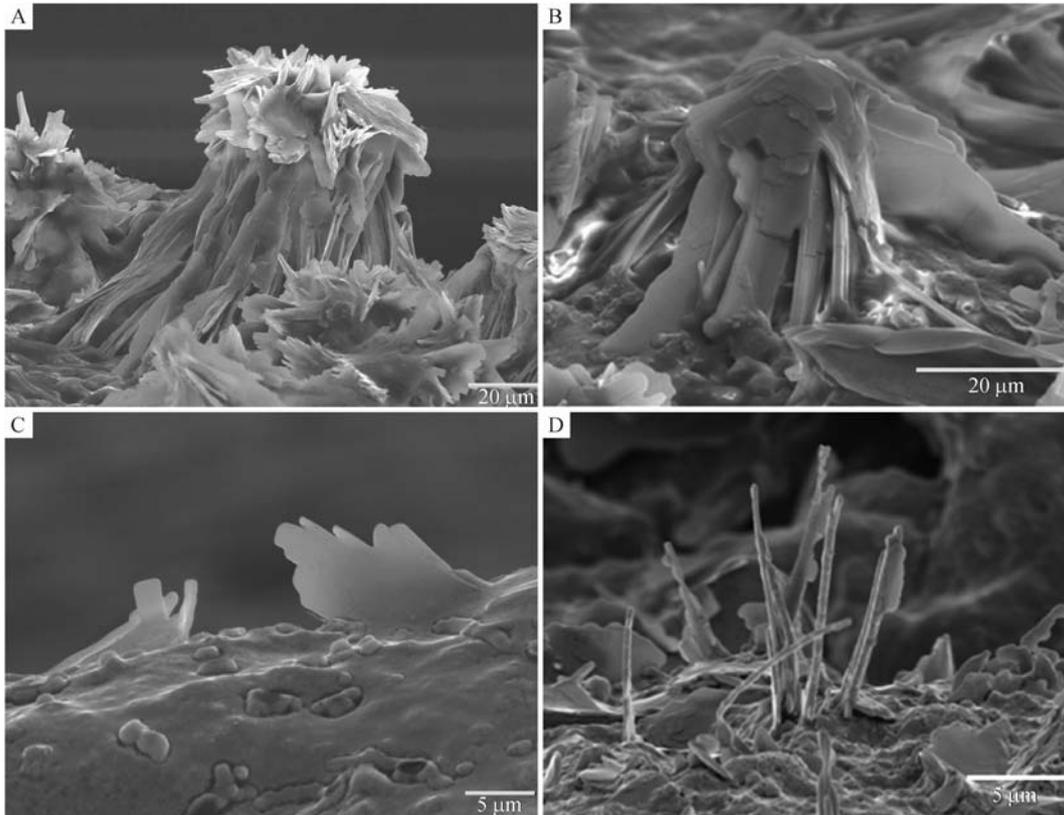
Fig. 7 **Statins treatment dissolves cholesterol crystals in human plaques.** A: Carotid plaque with clusters of cholesterol crystals protruding from the intima. B: Similar cholesterol crystals breaking down and dissolving following incubation with simvastain. C: Cholesterol crystals as commonly seen perforating the intimal surface in human carotid plaque from a patient not on statin therapy. D: Cholesterol crystals from patient on atorvastatin treatment prior to carotid endarterectomy demonstrates thinned down crystals with edges that have irregular borders and some are bent as typically seen with dissolving crystals. Modified and reproduced with permission[52].

showed a good renal outcome at 4 weeks; however, this treatment did not have a favorable effect on long-term renal outcome[55].

It is also helpful to minimize invasive therapies in patients known to have severe atherosclerosis or to investigate its presence before major cardiovascular procedures. Preoperative 64-slice multidetector CT scan has been used in CABG patients to evaluate the incidence of pathologic lesions of the aorta and its major branches. The finding of significant atherosclerosis can offer the opportunity to modify risk assessment, CABG procedure itself, perioperative management or follow-up plan in about half of patients[56]. Surgical removal or endovascular isolation of the source of emboli could offer a definitive treatment option. Surgeries to correct an embolic source (ligation and bypass, endarterectomy and graft revision) could be achieved with low mortality except when the embolic source is located in the suprarenal aorta[57].

Endovascular interventions with covered stents, endoluminal stent grafts, or stent graft components have been used to exclude the embolic source. Limited experience in patients with abdominal aortic aneurysm or those with mostly an aortoiliac embolic source showed significant healing of ischemic ulcerations and decrease of further embolization[58-59]. Finally, modifications in endovascular and surgical approaches can have additional benefits to the use of protection devices. These devices include distal filters and occlusion balloons that have been successfully used in carotid and to a lesser extent in renal artery interventions with a lower incidence of procedural adverse events[60-61]. The 'no touch' technique can be used as well during renal artery stenting to minimize rubbing of the guiding catheter against the aorta and reduce the potential for cholesterol embolization[29]. Of note, thromboembolic complications in off-pump coronary bypass operations are comparable with those in cardiopulmonary bypass operations[62].

Summary

Cholesterol crystal embolization results from plaque rupture with distal embolization of CCs that originate mainly in the aorta and iliac arteries. This can occur either spontaneously or from iatrogenic trauma and lead

to tissue injury. The embolic CCs can trigger tissue inflammation and a vasculitis-like picture. The most common clinical presentation are progressive renal dysfunction and livedo reticularis. Laboratory findings are not specific and non-invasive testing with ultrasound, CT and MRI are preferred to invasive angiography. Occasionally, histological examination may be necessary for a definite diagnosis. Use of fundoscopy can be valuable in making a diagnosis of CCE since it can detect CC emboli in the retinal arteries which is often associated with the systemic condition. Although undetected CCs showering may seem benign, it is important to recognize this entity because it often has a diffuse multi-organ involvement and carries a very high mortality related to cardiovascular events. Treatment is mainly supportive with considerations of using high dose statins and possibly steroids. Surgical removal or endovascular isolation of the source of emboli is an alternative therapeutic option but that carries a high risk. Overall, CCE can be a difficult diagnosis to make and is often associated with adverse outcomes.

Conflict of Interest

G.A. is a speaker and recipient of grants from Merck. He is a participant at Merck's US Thrombosis Advisory Board and Atherosclerosis Global Therapeutic Experts Forum. He is a speaker for Amgen, Daiichi Sankyo and consultant for Kowa pharmaceuticals.

F.G., D.V., J.K., S.D. N.T., and S.A. have no conflicts to declare.

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