Embolism from atherosclerotic plaque: Atheroembolism (cholesterol crystal embolism)

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INTRODUCTION — Aortic atherosclerotic plaques are a manifestation of systemic atherosclerosis. They are associated with general risk factors for atherosclerotic disease, including age, hypertension, and hypercholesterolemia, and are more common in patients with coronary artery disease [1,2].

Aortic atherosclerotic plaques are an important source of emboli, leading to cerebral (eg, transient ischemic attack, stroke), extremity or visceral embolization (picture 1) [3-6]. Embolic events can occur spontaneously or can be induced by interventions including cardiac catheterization, arteriography, peripheral interventions, intraaortic balloon pumping, and cardiac or vascular surgery [7,8].

The general manifestations and treatment of cholesterol crystal embolism, diagnosis and medical and surgical management will be reviewed. Thromboembolism from unstable aortic plaques is discussed elsewhere. (See "Embolism from aortic plaque: Thromboembolism".)

Specific considerations related to end-organ ischemia (kidney, gut, extremity) that may result from cholesterol crystal embolus are discussed in separate topic reviews.

ATHEROEMBOLISM VERSUS THROMBOEMBOLISM — Two types of emboli originate from atherosclerotic plaques: thromboemboli and atheroemboli (cholesterol crystal emboli). Although the underlying risk factors may be similar, the two can often be differentiated based upon associated conditions and clinical manifestations. This is an important distinction, since the prognosis and treatment differ. Thromboembolism from complex aortic plaques is common, particularly from thoracic aortic plaques. In comparison, cholesterol crystal embolism is fairly rare, but is probably under-recognized given its diverse presentations. (See 'Epidemiology and risk factors' below and "Embolism from aortic plaque: Thromboembolism".)

Although there is some overlap, these two disorders can be distinguished from each other. Thromboembolism occurs when thrombus, which is usually superimposed on an atherosclerotic plaque, dislodges due to plaque rupture or other forces. The thromboemboli tend to be single and lodge in medium or large arteries. Thromboemboli from aortic atherosclerotic plaque most often result in transient ischemic attack or stroke [3-6]. Acute ischemia of the extremities, intestines, or solid organs (eg, kidney, spleen) can also occur [9].

The term cholesterol crystal embolism is used synonymously with cholesterol embolism or

atheroembolism [10]. Cholesterol crystal embolism occurs when atherosclerotic plaque is disrupted and cholesterol crystals within the plaque or portions of the plaque embolize distally. The debris showers into the circulation partially or totally occluding arterioles that are <200 micrometers in diameter, leading to a myriad of occlusions that typically affect multiple organs. These characteristic sizes of atheroemboli were illustrated in an experimental study using human aortorenal endarterectomy specimens. Following ex vivo "angioplasty" of these specimens, thousands of fragments 20 to 40 micrometers in size, the approximate size of the human afferent arteriole, and hundreds >100 micrometers in size, were collected [11].

EPIDEMIOLOGY AND RISK FACTORS — Cholesterol embolization is most likely to occur in the male patient >50 years of age, with risk factors for atherosclerosis following cardiac catheterization or a vascular procedure. Cholesterol crystal embolism is strongly associated with older age, with the average age being 66 years in a review of 221 published cases [12]. Lighter-skinned individuals may be more often affected, but it is more likely that subtle skin manifestations are not recognized in patients with darker skin tones. (See 'Skin' below.)

The incidence and prevalence of cholesterol crystal embolism are unknown. The published estimates are limited by suboptimal or unclear diagnostic criteria (such as solely relying on elevation of serum creatinine concentration after a procedure), and infrequent biopsy data. The full manifestations of the syndrome are probably rare. (See 'Clinical manifestations' below.)

Cholesterol crystal embolization may arise spontaneously or as the result of instrumentation of the vasculature (eg, cardiac catheterization, arteriography, vascular surgery). The following observations are from some of the studies that have evaluated the incidence or prevalence of cholesterol crystal embolism:

- In a review of 519 patients with extensive thoracic aortic plaque on transesophageal echocardiography, cholesterol crystal embolism occurred in 1 percent of patients during a follow-up of more than three years [13].
- In a series of 1011 patients who underwent infrarenal aortic and infrainguinal vascular surgery or angiographic manipulation, clinical and pathologic evidence of cholesterol crystal embolism was found in 2.9 percent [14].
- Lower rates are seen after cardiac surgery (0.2 percent) [15]. In a prospective observational study of 1786 patients undergoing cardiac catheterization, definite cholesterol crystal embolism was observed in 0.8 percent [16].
- In a retrospective review of 493 patients who underwent aortoiliac stent placements, 72 bilateral, the incidence of atheroembolism was 1.6 percent [17].

Many cases of cholesterol crystal embolism are not recognized clinically [18]. This issue was addressed in a prospective study of 60 patients with an acute myocardial infarction, one-half of whom were treated with thrombolytic therapy [19]. All patients underwent coronary artery bypass graft surgery (CABG) within one month, and two muscle biopsy specimens and one skin biopsy specimen were obtained at the time of surgery. Seven patients (12 percent) had pathologic evidence of cholesterol crystal emboli in the muscle biopsy specimens, only one of whom had clinically evident disease.

This finding of asymptomatic disease is consistent with the prevalence of cholesterol crystal embolism in autopsy studies in unselected patients that range from 0.7 to 4 percent [15,20]. Even higher rates of cholesterol embolization (up to 75 percent) are reported in retrospective autopsy studies in patients selected for atherosclerotic risk factors or following surgery or instrumentation,

but these studies may overestimate the incidence of cholesterol crystal embolism due to selection bias [21].

In addition to asymptomatic disease, it is probable that clinical manifestations of cholesterol crystal embolism are ascribed to other causes. This may be most likely with acute renal failure, where acute kidney injury is much more common than cholesterol crystal embolism, which will not be diagnosed unless tissue is available for pathology if there are no other manifestations of this syndrome [22]. (See 'Renal' below.)

Risk factors for aortic atherosclerosis — Risk factors for developing cholesterol crystal embolism are largely those associated with developing general atherosclerotic disease such as smoking, hypercholesterolemia, hypertension, obesity, and diabetes. The data supporting these associations are discussed in detail separately. (See "Estimation of cardiovascular risk in an individual patient without known cardiovascular disease".)

The "classic" risk factors of hypertension, age, and smoking have been correlated with severe atherosclerotic plaque in the thoracic aorta. This relationship was demonstrated with transesophageal echocardiography (TEE) in a population-based study [23]. Among those with aortic plaque, the odds of having complex plaque increased as systolic blood pressure increased (OR 1.43 for each 10 mmHg increase, 95% CI 1.10-1.87). Complex aortic plaque also correlated with hypertension treatment, controlling for age and history of smoking.

Risk factors for embolization — The risk of cholesterol crystal embolization is directly related to the severity of atherosclerosis. Any factor that destabilizes atherosclerotic plaque can result in cholesterol crystal embolism. Embolization may be spontaneous or iatrogenic precipitated by vascular manipulation during arteriography or surgery. It was previously estimated that 50 to 60 percent of cases of cholesterol crystal embolization were spontaneous [14,24]. However, the increasing frequency of endovascular manipulations (eg, coronary, aortoiliac, renal) has increased the incidence of iatrogenic embolization [24,25]. In one retrospective review, spontaneous embolism occurred in only 25 percent of patients [26].

Abdominal aortic aneurysms are a known source of cholesterol emboli. In a prospective study of 660 patients with abdominal aortic aneurysm that were followed for 1 to 60 months (mean 15 months), cholesterol crystal embolization was diagnosed in 2.9 percent of the patients [27]. (See "Clinical evaluation of abdominal aortic aneurysm", section on 'Symptomatic'.)

Plaque characteristics and location — The risk of cholesterol crystal embolism in patients with aortic atherosclerosis is markedly increased if transesophageal echocardiography reveals protruding plaques, particularly if ≥4 mm in thickness; ulceration; or superimposed mobile thrombi [5,9,28-32].

A correlation between complex plaque seen on two-dimensional transesophageal echocardiography (2D-TEE) and embolization phenomena was first noted in 1990 [30]. Subsequent 2D-TEE studies found that complex plaques may give rise to either cholesterol crystal emboli or thromboemboli (picture 2 and movie 1). In a few case reports, cholesterol crystal embolism to the skin and kidneys was proven by biopsy in patients with complex plaques in the descending thoracic aorta on 2D-TEE [31,32]. In another report, transesophageal echocardiography demonstrated mobile particulate matter in transit from a complex plaque in a patient who subsequently died after multisystem involvement from cholesterol crystal embolism (figure 1) [33].

Plaque in the aortic arch is implicated as a risk factor for cerebral embolization. However, data are conflicting. In longitudinal population-based studies in non-selected individuals, complex aortic atherosclerosis does not appear to be associated with an increased risk of primary stroke [34].

However, most reports evaluating secondary stroke risk have found that complex aortic

atherosclerosis is a risk factor for recurrent stroke. This may be due to selection bias as the studies linking aortic atheroma and secondary stroke were usually performed in patients referred for TEE to evaluate a cardiac source of emboli rather than in a random population sample.

Mechanistically, aortic plaque may be both a source of cerebral emboli and a marker of generalized atherosclerosis. Studies of aortic arch plaque have found a 12 to 14 percent risk of cerebral embolization, particularly when the plaque is ulcerated or mobile. On the other hand, aortic plaque may be a marker of aging and age is an independent predictor of cerebrovascular events [35].

Atherosclerotic plaque in the thoracic aorta is typically associated with distal embolization (abdominal organs, lower extremities). However, retrograde flow from complex descending thoracic aortic plaques may be a source of cranial or upper extremity embolization. In a study of 94 patients using transesophageal echocardiography, retrograde diastolic flow reached the left subclavian artery in 60 percent, the left common carotid artery in 26 percent, and the brachiocephalic trunk in 14 percent [36].

The abdominal aorta and iliac arteries are commonly identified as a source for lower extremity cholesterol crystal embolization. In one surgical series of 62 patients, the aorta or iliac arteries were identified angiographically as the embolic source in 80 percent of patients [24].

Atherosclerotic plaque in the femoral, popliteal, or subclavian arteries may also be a source of extremity embolization.

Instrumentation — Iatrogenic embolism is typically due to vascular manipulation during arteriography or surgery. Surgical procedures may disrupt atherosclerotic plaque as vessels are dissected, cross-clamped, or as an arteriotomy is made. Trauma is an unusual cause [24].

Arteriography is a more common iatrogenic cause than surgery, accounting for as many as 85 percent of iatrogenic cases [14]. The source of the emboli in a review of 29 patients was the abdominal aorta (16 patients), iliac arteries (7 patients) and femoropopliteal arteries (6 patients) [14]. Patients with atherosclerotic renal artery stenosis often have diffuse atherosclerosis and are at a relatively high risk for cholesterol crystal embolism after renal arteriography, with an overall incidence of about 2 percent [37].

The effect of arterial manipulation has been illustrated in several studies. In a prospective series of 1000 patients who underwent percutaneous coronary interventions, guiding catheter placement was associated with visible scraping of debris from the walls of the aorta in more than one-half of the patients [38]. Clinical cholesterol crystal embolism was not seen, however, as ischemic events were not associated with visualization of debris in the catheter. Similarly, with renal artery angioplasty with stenting, grossly visible material (cholesterol crystals, atheromatous material and thrombus) are found in the embolic protection filter in 45 to 60 percent of cases [39,40]. (See "Clinical characteristics of renal atheroemboli".)

Anticoagulation/thrombolytic therapy — Cholesterol crystal embolism has been reported after the use of thrombolytic agents or anticoagulants (primarily heparin and warfarin). However, a causal relationship between the use of these medications and cholesterol crystal embolism has not been established and, based on available evidence, the overall risk appears to be low.

In the 40 years since the introduction of thrombolytic therapy, a total of 30 cases as a complication of thrombolysis have been reported; 28 patients received a thrombolytic agent for acute myocardial infarction and 2 patients for deep venous thrombosis [41,42]. These case reports gave the impression that there might be a causal relationship between thrombolysis and cholesterol crystal embolism. However, there is no evidence to suggest that lysis of thrombus overlying atherosclerotic plaque leads to plaque destabilization and atheroembolism. There are no large-scale

clinical trials that specifically addressed the issue of cholesterol crystal embolism in the setting of thrombolytic therapy. One small study of 60 patients found no differences in the rate of cholesterol crystal embolism between the patients who received thrombolysis and those who did not. The presence or absence of cholesterol crystal embolism in this study was based upon skin and muscle biopsies [19]. However, given the low incidence of embolism and the small number of patients in the study, a significant difference may not have been detectable.

Cholesterol crystal embolism has also been blamed on therapy with anticoagulant drugs, particularly heparin or warfarin, with plaque hemorrhage as the putative precipitating factor [43,44]. However, it is unclear if cholesterol crystal embolism was caused by anticoagulants or it simply occurred in patients who happened to be on anticoagulation therapy. Trials that have randomly assigned patients with documented aortic plaque identified by transesophageal echocardiography to anticoagulant therapy have not identified an increased risk for atheroembolism [13,16,45,46]. Thus, the putative risk associated with anticoagulation therapy appears to be low.

CLINICAL MANIFESTATIONS — The variability in clinical manifestation is related to the location of the embolic source, extent of embolization, whether there is partial or complete occlusion of the affected vessels, and the presence or absence of preexisting disease in the affected vascular bed (eg, peripheral artery disease).

Atheroemboli from the aortic arch typically embolize to the brain, eye, or upper extremity while descending thoracic or abdominal aortic plaque causes gastrointestinal or lower extremity symptoms and signs. Retrograde embolization from the thoracic aorta can also occur. (See 'Plaque characteristics and location' above.)

The presenting symptoms of cholesterol crystal embolism may be subtle and nonspecific. As an example, 21 percent of patients in a review of 221 cases presented with systemic symptoms of fever, myalgias, headache, and weight loss [12]. Often there is a delay between the embolic event and subsequent symptoms. In a review of histologically proven cholesterol embolization, skin signs developed more than 30 days after a precipitating event in 50 percent of patients [47].

More dramatic clinical presentations are generally due to a diffuse showering of larger, atheromatous debris originating from usually aortic plaque. The emboli may lodge into the renal, mesenteric, pelvic, carotid, coronary, or extremity vascular beds [48]. Classic manifestations include "blue toe syndrome," livedo reticularis, acute or subacute renal failure, and intestinal ischemia. Other manifestations include gastrointestinal bleeding and pancreatitis.

Skin — Skin findings are the most common clinical sign of cholesterol crystal embolism, occurring in 34 percent of patients in one systematic review [12]. In this study, the most frequent findings included livedo reticularis (16 percent), gangrene (12 percent), cyanosis (10 percent), skin ulcer (6 percent), purpura or petechiae (5 percent) and firm, painful erythematous nodules (3 percent) [12]. Splinter hemorrhages have also been described as a possible cutaneous manifestation of cholesterol crystal embolization [49]. Gangrene and ulcerations typically affect the toes but may extend to more proximal portions of the lower extremities. (See "Clinical manifestations and evaluation of chronic critical limb ischemia" and "Treatment of lower extremity critical limb ischemia".)

These classic skin findings in cholesterol crystal embolism commonly occur in areas where the arterial pulse is palpable, since the embolization is to smaller arteries [12,47,50]. However, the arterial pulse may not be palpable in patients who also have underlying peripheral artery disease. (See "Noninvasive diagnosis of arterial disease" and 'Treatment' below.)

Cholesterol crystal embolization to the skin of the genitalia is rare, but when it occurs, can lead to severe scrotal or penile skin loss [51-53]. This devastating complication has been reported following open and, more recently, endovascular repair of abdominal aortic aneurysm [53].

Livedo reticularis — Livedo reticularis is a reticulated, mottled or erythematous skin discoloration which blanches on pressure (picture 3). It may be red or blue, and even ulcerated, depending on the degree of blood flow compromise and oxygen desaturation through the affected area. Livedo reticularis is not specific for atheroembolism and has an extensive differential diagnosis. In patients with cholesterol crystal embolization, livedo reticularis is usually bilateral and is typically found on the feet and lower legs but may extend toward the thighs, buttocks, and the back. Upper extremities are less commonly involved.

In patients undergoing abdominal aortic aneurysm repair, livedo reticularis may appear on the back and the buttocks due to cholesterol embolization into the branches of the internal iliac arteries.

Blue toe syndrome — Although cholesterol crystal embolization is often referred to as the "blue toe syndrome" (picture 4), blue skin discoloration is less common than other skin findings. In the overall population of patients with cholesterol embolization syndrome, skin manifestations are seen in only about a third of such patients, and of these, blue toes are present in 10 to 15 percent [12,18,47].

- In a retrospective review of 78 patients with cutaneous manifestations of cholesterol crystal embolization, blue toes were noted in 14 percent of the patients. More common skin manifestations were livedo reticularis (49 percent), gangrene (35 percent), cyanosis (28 percent) and ulceration (17 percent) [47].
- In another study of 221 patients, skin manifestations were present in 75 patients. Of these 75, blue toes were observed in 11 patients [12].

Renal — Acute kidney injury is a common manifestation of cholesterol crystal embolism [26,54]. The characteristics of renal involvement are discussed in detail separately (picture 5A-B). (See "Clinical characteristics of renal atheroemboli".)

Summarized briefly:

- Acute kidney injury is present in 25 to 50 percent of cases [12,15,24]. Renal disease most often occurs after invasive vascular procedures, but can occur spontaneously. In such patients, the diagnosis may be difficult to establish without biopsy unless other manifestations of crystal embolism are present.
- Because the cholesterol crystal emboli are irregularly shaped and nondistensible, and typically do not completely occlude larger vessels, the renal manifestations are those of distal parenchymal ischemia usually manifested as a bland sediment rather than renal infarction as seen with thromboemboli, which present with flank pain, hematuria that may be gross, and markedly elevated serum lactate dehydrogenase.
- When acute kidney injury occurs after arteriography, the primary differential diagnosis is contrast nephropathy and cholesterol crystal embolism. Unless there are other signs of cholesterol crystal embolism, the two disorders are distinguished by differences in the clinical course. Contrast nephropathy typically begins to recover within three to five days, while cholesterol crystal embolism shows at best an incomplete recovery and there may be a stuttering course with further showers of cholesterol crystals. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy".)
- Although not a common manifestation of cholesterol crystal embolism, rhabdomyolysis has been reported in association with massive cholesterol crystal embolism and can lead to heme-pigment-associated acute kidney injury [55]. Rhabdomyolysis presents with elevated serum

muscle enzymes (including creatine kinase), red to brown urine due to myoglobinuria if there is persistent renal function, and electrolyte abnormalities. Peak serum creatine kinase levels depend upon the volume of muscle breakdown and the muscle mass of the patient. (See "Clinical features and diagnosis of heme pigment-induced acute kidney injury (acute renal failure)".)

Gastrointestinal — Atheroembolism to the mesenteric circulation most commonly involves the colon, small bowel, and stomach [56]. The pancreas, liver, and gallbladder also may be affected [57]. (See "Acute mesenteric ischemia" and "Colonic ischemia".)

Gastrointestinal manifestations include abdominal pain, diarrhea, and, in about 10 percent of patients, bleeding [12,56,58]. Bleeding may originate from any site in the gastrointestinal tract, including the stomach [59]. Other manifestations of cholesterol crystal embolism include necrotizing pancreatitis, focal hepatic cell necrosis, and acalculous necrotizing cholecystitis. Intestinal infarction has a poor prognosis, with reported mortality rates ranging from 38 to 81 percent [12,60].

Upper endoscopic findings of nonspecific entities such as gastritis may be erroneously diagnosed [59]. A definitive diagnosis can only be established by examination of a biopsy specimen.

Central nervous system — Central nervous system manifestations of atheroembolism may include amaurosis fugax, transient ischemic attack, stroke, confusional state, headache, dizziness, or organic brain syndrome. Embolization to the spinal cord is rare but can lead to lower extremity paralysis

Transient ischemic attack due to atheroembolic debris is more commonly associated with carotid atherosclerotic disease, and carotid thrombosis or thromboembolism can lead to hemispheric stroke. (See "Etiology and classification of stroke", section on 'Embolism'.)

There are conflicting data regarding the stroke risk associated with aortic atherosclerosis [4,5,34,61-65]. Large protruding plaques in the aortic arch, particularly mobile plaques, in our opinion, are an important cause of brain pathology. In one retrospective review of 29 patients with cholesterol emboli in the brain identified on autopsy, encephalopathy presumably due to ischemia was the predominant clinical finding and was most likely due to bilateral diffuse embolization from the identified aortic plaque disease [66].

In clinical longitudinal population studies in unselected patients, complex aortic atherosclerosis does not appear to be associated with an increased risk for primary ischemic stroke [34,62,63]. However, most studies have found that complex aortic atherosclerosis is a risk factor for recurrent stroke [4,5,64,65].

The range of findings is illustrated by the following studies:

- A prospective study examined the frequency and thickness of atherosclerotic plaques in the ascending aorta and proximal arch in 250 patients admitted to the hospital with ischemic stroke and 250 consecutive controls, all over the age of 60 years [5]. Atherosclerotic plaques ≥4 mm in thickness were found in 14 percent of patients compared with 2 percent of controls, and the odds ratio for ischemic stroke among patients with such plaques was 9.1 after adjustment for atherosclerotic risk factors. In addition, aortic atherosclerotic plaques ≥4 mm were much more common in patients with brain infarcts of unknown cause (relative risk 4.7).

- In contrast, a population-based study of 1135 subjects who had transesophageal echocardiography (TEE) found that complex atherosclerotic plaque (>4 mm with or without

mobile debris) in the ascending and transverse aortic arch was not a significant risk factor for cryptogenic ischemic stroke or TIA after adjusting for age, gender, and other clinical risk factors [62]. However, there was an association between complex aortic plaque and non-cryptogenic stroke. The investigators concluded that complex aortic arch debris is a marker for the presence of generalized atherosclerosis.

Methodologic differences are a potential explanation for the discrepant results of these reports assessing the risk of ischemic stroke related to aortic atherosclerosis, as the earlier case-control studies may have been skewed by selection and referral bias. However, many patients with aortic atherosclerosis also have cardiac or large artery lesions, a problem that may confound purely epidemiologic studies

Ocular signs — Hollenhorst plaques are bright, refractile lesions in the retina indicative of cholesterol crystal embolization from a proximal atherosclerotic source (picture 6) [67].

The most common proximal source is the carotid artery [68,69]. In a review of 130 patents with Hollenhorst plaque or retinal artery occlusion (amaurosis excluded), 61 percent complained of ocular symptoms including eye pain, blurred vision or other atypical visual symptoms [70]. Of the 98 patients who underwent carotid duplex, all had some evidence of carotid stenosis ipsilateral to the ocular findings but the degree of stenosis was less than 60 percent in 90 of the 130 patients. Over a mean of 22 months, no patient suffered from a transient ischemic attack (including amaurosis fugax) or stroke. Evaluation of the more central vasculature was performed in about 20 percent of the patients and, although some minor valvular problems were found, a cardiac or aortic source for the retinal findings was not found.

Cholesterol embolization resulting in Hollenhorst plaques can occur following arteriography or cardiac catheterization, vascular surgery, or trauma. The mere finding of Hollenhorst plaques in a patient presenting with suspected cholesterol embolization syndrome should not be used to confirm that the acute clinical presentation is due to cholesterol emboli. A finding of Hollenhorst plaque may represent a prior event [71,72]. In one study, serial funduscopic examination found persistence of Hollenhorst plaques for over a year [69]. Moreover, about one-third of patients who have Hollenhorst plaques are asymptomatic. Thus, additional evaluation may be needed to confirm the diagnosis of acute cholesterol embolization syndrome. (See 'Diagnosis' below.)

Other — Other vascular beds including coronary, pulmonary, prostate, thyroid and adrenal glands may rarely be affected with diagnosis usually established at autopsy.

DIAGNOSIS — A diagnosis of cholesterol crystal embolization should be highly suspected in a patient with known atherosclerotic disease and a classic history: the development of renal failure, abdominal pain or diarrhea, typical skin findings or a finding of Hollenhorst plaques of the retina following arteriography, cardiac catheterization, vascular surgery, or trauma to the abdomen. (See 'Clinical manifestations' above.)

Laboratory testing is generally nonspecific and may show elevations in the white blood cell count, decreased red blood cell count, or thrombocytopenia. Inflammation markers including elevated erythrocyte sedimentation rate, C-reactive protein and fibrinogen have been associated with atheroembolism [16]. Other abnormalities may include transient hypocomplementemia and eosinophilia.

Because there is an association between occlusive diseases in large peripheral arteries and cholesterol crystal embolization to smaller arteries, patients with extremity embolism should undergo noninvasive vascular testing to identify the presence of hemodynamically significant proximal peripheral artery disease. Even when a stenotic peripheral artery may not be the source of cholesterol crystal embolism, arterial revascularization may improve clinical outcomes. (See

'Revascularization' below.)

Specific abnormalities may indicate end-organ dysfunction such as increased creatinine or eosinophiluria if the kidneys are involved [73-76], increased amylase with pancreatic (and possibly bowel) involvement, elevated transaminases with hepatic involvement or elevated creatine kinase and myoglobinuria with sufficient muscle involvement.

Imaging — Plaques in the aorta can be visualized, characterized and quantified by a variety of imaging techniques; however, the index plaque that is the cause of the cholesterol crystal embolization is rarely determined. The diagnosis is more difficult in patients without typical clinical features, particularly if cholesterol crystal embolism has occurred spontaneously. However, the identification of complex aortic plaque or multiple ischemic strokes on imaging studies may permit a presumptive diagnosis to be made [5,28,29].

Plaques can be simple or complex (figure 2). Simple plaques are characterized by wall thickness <4 mm and the absence of mobile components. Complex plaques are ≥4 mm in thickness, and may exhibit irregular borders, ulceration and mobile components which represent superimposed thrombus. Complex plaques are associated with an increased propensity for embolization. (See 'Plaque characteristics and location' above.)

Transesophageal echocardiography, primarily two-dimensional (2D) transesophageal echocardiography (TEE), is the first-line diagnostic modality to identify a thoracic aortic source of atheroembolism. Real-time three-dimensional transesophageal echocardiography (3D-TEE) provides very detailed information on aortic plaque location and morphology (picture 7 and movie 2). Transthoracic echocardiography, abdominal ultrasound, and endoscopic ultrasound (picture 8) of the upper gastrointestinal tract have occasionally incidentally identified atherosclerotic plaques in the thoracic or abdominal aorta.

Compared with TEE, computed tomography (CT) (picture 9 and movie 3) and magnetic resonance imaging (MRI) (picture 10) are less invasive and more complete evaluations of the extent of atherosclerosis in the aorta. CT and MRI have several advantages over TEE [77,78]. These radiologic techniques are better than TEE for imaging aortic branches. In addition, they can image the entire abdominal aorta. In comparison, only the very proximal abdominal aorta between the diaphragm and the ostium of the superior mesenteric artery can be seen with TEE.

Conventional arteriography has low sensitivity for detection of plaques and often fails to identify plaques detected by other imaging techniques and should be avoided given the potential disruption of atherosclerotic debris with instrumentation [79]. (See 'Instrumentation' above.)

Radiologic studies of the brain may help suggest the diagnosis in demonstrating multiple small ischemic lesions. (See "Neuroimaging of acute ischemic stroke".)

Biopsy and pathologic findings — Biopsy is the only definitive means of confirming the diagnosis of cholesterol embolization syndrome. Thus, biopsy should be performed whenever the diagnosis is in doubt and when the specimen can safely be obtained from the patient. Histopathologic examination of amputated body parts or embolectomy specimens for cholesterol emboli pose no additional risk to the patient and should be performed if the diagnosis is suspected. Skin and skeletal biopsies are less invasive than renal and gastrointestinal biopsies.

The histologic hallmark of cholesterol crystal embolism is the presence of "ghosts" of cholesterol crystals or cholesterol clefts within arterioles, since the cholesterol crystals are dissolved during tissue fixation (picture 5A-B). The cholesterol clefts are crescentic (with pointed ends) or elongated ovoid spaces present in small or medium-sized arteries or arterioles. Inflammatory or fibrous intimal proliferation develops rapidly, and may be the cause for vascular occlusion and

resultant ischemic tissue damage [80].

Cholesterol clefts have also been demonstrated in the pulmonary arteries of patients with cholesterol crystal embolism. Since pulmonary arterial atherosclerosis is rare (eg, in end-stage Eisenmenger syndrome), the crystals presumably pass through the systemic capillary bed into the venous system and lungs. In a case report, cholesterol crystal emboli were seen in 25 percent of the small pulmonary arteries in a patient with atheroembolic disease [81].

Differential diagnosis — The diagnosis is often difficult to establish when the presenting symptoms and signs of cholesterol crystal embolism are subtle and nonspecific. Cholesterol crystal embolism needs to be distinguished from thromboembolism given differences in treatment. (See "Embolism from aortic plaque: Thromboembolism".)

Because of its many differing effects, cholesterol crystal embolism may be included as one of the "great imitators," (such as tuberculosis, brucellosis) given its often nonspecific symptoms, leading it to be confused with a number of other diseases, including vascular diseases such aortic dissection, and tumors such as left atrial myxoma, lymphoma, and renal cell carcinoma [48]. The differential diagnosis includes many systemic illnesses including cyanotic congenital heart disease, secondary syphilis, and pheochromocytoma [60].

There is also an extensive differential diagnosis of livedo reticularis that includes Raynaud's phenomenon, vasculitis (polyarteritis nodosa, systemic lupus, dermatomyositis, leukocytoclastic angiitis, rheumatoid vasculitis, thromboangiitis obliterans), infection (syphilis or tuberculosis), cryoglobulinemia, antiphospholipid syndrome, and polycythemia vera. A familial form called Sneddon's syndrome is seen in association with cerebrovascular disease.

Among patients who develop acute kidney injury, particularly if the sediment is relatively bland, the differential renal diagnosis includes contrast nephropathy and acute kidney injury, both of which are typically reversible. (See "Clinical characteristics of renal atheroemboli".)

TREATMENT — Treatment for cholesterol embolization comprises managing cardiovascular risk factors, management of end-organ ischemia, and prevention of recurrent embolization.

Risk factor management — Patients with cholesterol crystal embolism should be aggressively treated for secondary prevention of cardiovascular disease [82]. These modalities include aspirin, statins, blood pressure control, cessation of smoking, and, in patients with diabetes, glycemic control. (See 'Statin therapy' below and "Secondary prevention of cardiovascular disease: Risk factor reduction".)

Managing ischemia — The management of the microvascular obstruction leading to end-organ ischemia varies depending upon the vascular bed affected, but is primarily supportive. The general principles of managing transient ischemic attack, stroke, renal embolization or infarction, gastrointestinal ischemia or infarction, and extremity ischemia are discussed in separate topic reviews.(See "Diagnosis and treatment of renal infarction" and "Acute arterial occlusion of the lower extremities (acute limb ischemia)" and "Acute mesenteric ischemia" and "Initial evaluation and management of transient ischemic attack and minor stroke".)

The inflammatory reaction that results from cholesterol crystal embolization is essentially a foreign body reaction to the cholesterol crystals which are resistant to breakdown by macrophages. Arterioles that are not immediately occluded may occlude as a chronic inflammatory infiltrate fills the lumen. Given this pathologic mechanism, various antiinflammatory and antithrombotic agents have been used in an attempt to lessen the inflammatory reaction to prevent thrombosis.

There are no large trials evaluating antiinflammatory therapies for treating cholesterol crystal embolism. Isolated reports in small numbers of patients using steroids [83-88], iloprost [89,90], and

LDL apheresis [91-93], have shown modest success.

The inflammatory nature of cholesterol crystal embolism results in pain that is often out of proportion to the apparent degree of tissue ischemia and pain management is of critical importance. (See "Overview of the treatment of chronic pain" and "Pain control in the critically ill adult patient".)

Aggressive saline hydration is the primary initial therapy of myoglobinuria, lowering the risk of induction of acute kidney injury. Other treatments may include bicarbonate or mannitol. The prevention and treatment of heme pigment-induced acute kidney injury is discussed in detail elsewhere. (See "Prevention and treatment of heme pigment-induced acute kidney injury (acute renal failure)".)

Preventing recurrent embolization — The optimal treatment to prevent recurrent cholesterol crystal embolization is not clear. Secondary prevention seems warranted, particularly since aortic plaques ≥4 mm in size appear to be associated with an increased risk of recurrent stroke [6,94,95]. In patients whose cholesterol embolization syndrome was precipitated by instrumentation (such as arteriography, cardiac catheterization or vascular surgery), any further invasive imaging or treatment should be avoided unless absolutely necessary. Noninvasive ultrasound, CT or MRI imaging should replace the invasive techniques whenever possible. When arterial cannulation is absolutely necessary, alternative access routes should be considered (eg, cardiac catheterization via radial artery approach in a patient with extensive plaques in the descending thoracic aorta).

Statin therapy — Statin therapy may decrease the risk of future embolization. Statins lower LDL-cholesterol and have a variety of other effects, one of which appears to be plaque stabilization. In a retrospective study of 519 patients with severe thoracic aortic plaque cited, statin therapy was associated with a significantly lower rate of recurrent stroke and thromboembolization [13]. However, the number of patients with atheroembolization was too small (five) for subset analysis. On multivariate analysis, the protective effect seen with statin therapy was not present for patients taking warfarin or antiplatelet agents. (See "Mechanisms of benefit of lipid-lowering drugs in patients with coronary heart disease", section on 'Plaque stabilization'.)

Antithrombotic therapy — Anticoagulant therapy for the treatment of cholesterol crystal embolism remains controversial. Although it seems intuitive that anticoagulation would improve arterial patency, the obstruction is mostly due to the atheroembolic debris and the inflammatory reaction it incites, and not thrombus. Another important consideration is the association between anticoagulant and antithrombotic therapy and the development of cholesterol crystal embolism; however, due to paucity of data, a causal relationship between cholesterol crystal embolism and anticoagulation and/or thrombolytic therapy can be neither proven nor refuted with certainty. (See 'Anticoagulation/thrombolytic therapy' above.)

There are no randomized trials that have evaluated the role of antithrombotic therapy in patients with aortic atheroma [94,96]. Nonrandomized retrospective studies have shown a benefit of oral anticoagulation over aspirin in patients with mobile thrombi in the aortic arch. Based on this low quality evidence, the 2008 ACCP guidelines panel suggested oral anticoagulation or antiplatelet agents for patients with cryptogenic stroke and mobile aortic arch thrombi [96]. (See "Cryptogenic stroke", section on 'Prevention and treatment'.)

However, the 2008 ACCP guidelines stated that the hemorrhagic complications may outweigh the benefits of anticoagulation [96]. Other studies have not shown a benefit to anticoagulation. In a retrospective review of 519 patients with complex plaque, cholesterol crystal embolism occurred in only five (1 percent) during a follow-up of more than three years [13]. The risk was similar in the patients treated (2 of 206) and not treated with warfarin (3 of 313). This rate is similar to that noted in the Stroke Prevention in Atrial Fibrillation (SPAF-III) trial (1 of 134 warfarin-treated

patients), most of whom had severe atherosclerotic plaques on transesophageal echocardiography [45,46].

In our practice, we do not routinely use anticoagulants in patients who are diagnosed with cholesterol crystal embolism unless they have other indications for anticoagulation (such as atrial fibrillation or mechanical prosthetic valve). Definitive recommendations regarding the use of anticoagulant in this context should await the results of an ongoing randomized trial comparing oral anticoagulant with antiplatelet therapy in patients with thoracic aortic plaque. The ARCH trial is an ongoing international randomized controlled study comparing warfarin with antiplatelet therapy (aspirin in combination with clopidogrel) for the prevention of stroke in patients with aortic arch atheroma that is either mobile or ≥4 mm thick [97].

It is important to emphasize that the package insert for warfarin explicitly states that warfarin therapy may increase the risk of cholesterol crystal embolism and that discontinuation of warfarin is recommended when cholesterol crystal embolism is observed [98].

Plaque removal or exclusion — Given the poor outcomes associated with cholesterol crystal embolism, surgical plaque removal (endarterectomy) or exclusion of the plaque (ligation and bypass, endovascular exclusion) may be indicated if a clear embolic source is identified, the source is surgically accessible, and the patient is an appropriate candidate for surgery. Patients with lower extremity symptoms and an infrarenal source for embolism may have more favorable outcomes [99].

In a prospective study of 100 patients who underwent surgery over a 12-year period following identification of the embolic source, occlusive aortoiliac disease (47 patients) and small aortic aneurysms (20 patients) were the most commonly identified embolic sources [100].

The most common surgical treatment was aortic bypass. Other procedures included aortoiliac endarterectomy with patching, femoral or popliteal endarterectomy, and infrainguinal or upper extremity bypass. (See "Treatment of lower extremity critical limb ischemia" and "Upper extremity peripheral artery disease".)

In this study the reported outcomes were:

- Postoperative mortality – 11 percent (all had a suprarenal aortic thrombus preoperatively)
- Survival rates at one, three and five years – 89, 83, and 73 percent, respectively
- Toe and leg amputations – 9 and 10 percent, respectively
- Hemodialysis – 10 percent
- Recurrent emboli – 5 percent within eight months of surgery with no further emboli over the next three years

In another surgical series of 62 patients who underwent surgery at one institution, bypass grafts were inserted in 42 patients after exclusion of the native diseased artery, 20 had endarterectomies (6 of them with bypass grafts), and 5 were treated medically [24]. The 30-day mortality rate was 5 percent. "Minor" amputation was required in 19 patients (31 percent), and leg amputation in 2 patients. Limb salvage was possible in 86 of 88 limbs. There were no postoperative embolic incidents in the involved limbs during a mean follow-up of 20 months.

Covered stents — More recently, covered stents and endografts have been used to exclude the involved arterial segment in a small number of patients with aortic or iliac artery sources of cholesterol crystal embolism [27,101]. The disadvantage of this technique compared with open surgery is a greater risk for recurrent embolization related to the intraluminal manipulation of

guidewires [17]. Definitive recommendations for the use of covered stents are not possible at this time.

Revascularization — For patients with lower extremity cholesterol embolism and a hemodynamically significant proximal stenosis (that may or may not be the source of embolism), arterial revascularization can restore normal pressures, improve distal perfusion and may improve pain. (See 'Managing ischemia' above.)

Surgical (eg, bypass) or endovascular (eg, stent) management may be appropriate depending on the location of the obstruction. Percutaneous angioplasty and stenting, mostly of the iliac and femoral arteries, have been performed in a small number of patients without causing recurrent embolization [100,102]. The decision on whether to perform revascularization in patients with cholesterol embolization syndrome should also take into account the severity and duration of ischemic symptoms.

PROGNOSIS — The prognosis in medically treated patients with cholesterol crystal emboli is poor, in part because of severe underlying atherosclerosis [103]. Acute, in-hospital mortality was 16 percent (4 of 25) in one series [16], but mortality rates may be as high as 80 percent when cases that are diagnosed post-mortem are included [12].

SUMMARY AND RECOMMENDATIONS

- Atheroembolism, also known as cholesterol crystal embolism or cholesterol embolism refers to arterio-arterial embolism of cholesterol crystals or small pieces of atheromatous material originating from an atherosclerotic plaque usually from the aorta but occasionally from other arteries. Cholesterol crystal embolism results in partial or total occlusion of small arteries, leading to tissue or organ ischemia. (See 'Introduction' above.)

- Risk factors for atheroembolism include patient factors such as hypertension, advancing age, smoking, hypercholesterolemia, obesity, and diabetes. Anatomic factors associated with the aortic atherosclerotic plaque such as plaque thickness ≥4 mm, plaque ulceration, or the presence of mobile debris increases the risk for embolization. (See 'Epidemiology and risk factors' above.)

- The clinical diagnosis of cholesterol crystal embolism should be suspected in patients with known atherosclerotic disease and the development of renal failure, transient ischemic attack, cerebral infarction, signs of intestinal ischemia, digital ischemia, typical skin findings or Hollenhorst plaques in the retina particularly following arteriography, cardiac catheterization, vascular surgery, or trauma to the abdomen. The diagnosis is more difficult in patients who do not have these features, particularly if cholesterol crystal embolism has occurred spontaneously. (See 'Clinical manifestations' above.)

- The presence of complex aortic plaque on imaging studies supports a diagnosis. Atherosclerotic plaques can also be seen using transthoracic echocardiography, abdominal ultrasound and endoscopic ultrasound of the upper gastrointestinal tract. (See 'Imaging' above.)

- Laboratory testing is generally nonspecific but may indicate the effects of end-organ ischemia. A definitive diagnosis depends upon pathologic specimens. Biopsy should be performed whenever the diagnosis is in doubt and when the specimen can safely be obtained from the patient; debrided or amputated tissue and thrombectomy specimens should be sent for pathologic examination since these represent no risk to the patient. The histologic hallmark of cholesterol crystal embolism is the presence of "ghosts" of cholesterol crystals or cholesterol clefts within arterioles. (See 'Biopsy and pathologic findings' above.)

- The treatment of cholesterol crystal embolism is primarily medical, consisting of risk-factor reduction. Statin therapy is indicated as part of risk-factor reduction and appears to reduce the rate of recurrent embolism. (See 'Statin therapy' above.)

- Surgical or endovascular treatment may be indicated if a clear embolic source is identified, the source is anatomically suitable, and the patient is an appropriate candidate for surgery. For patients who meet these criteria, we suggest surgical or endovascular treatment to remove or exclude the embolic source (**Grade 2C**). (See 'Treatment' above.)

- We suggest **not** routinely anticoagulating patients who are diagnosed with cholesterol crystal embolism (**Grade 2C**). Anticoagulation with heparin, warfarin, and use of thrombolytic therapy are all associated with the development of cholesterol embolism, although a causal relationship has never been demonstrated. However, patients with another indication for anticoagulation, such as thromboembolism or deep vein thrombosis, should be treated. (See 'Managing ischemia' above.)

- The prognosis in patients with cholesterol crystal embolism correlates with the degree of the underlying atherosclerosis, and is overall poor. (See 'Prognosis' above.)

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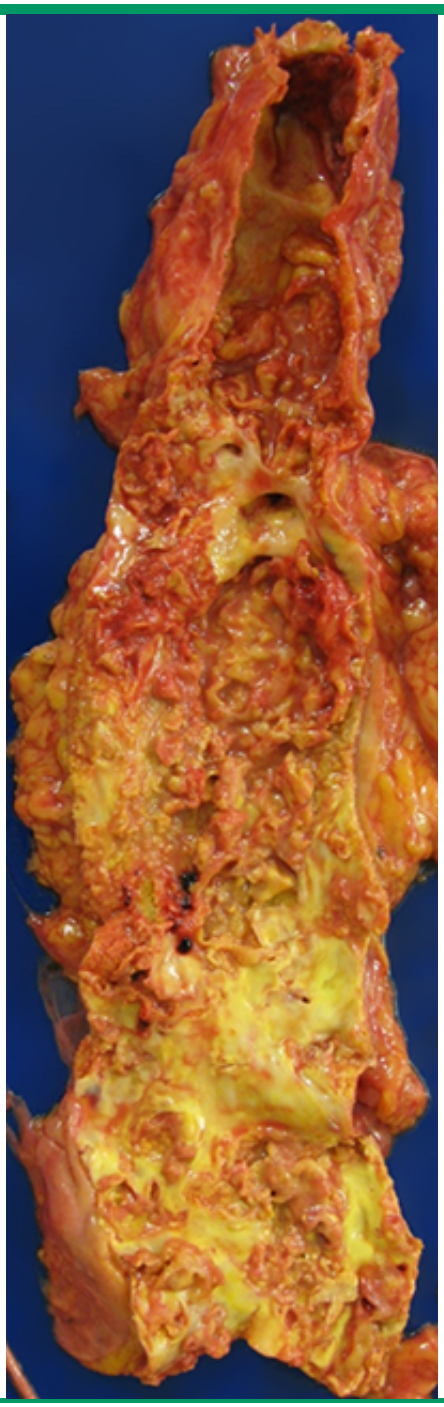
Topic 8184 Version 3.0

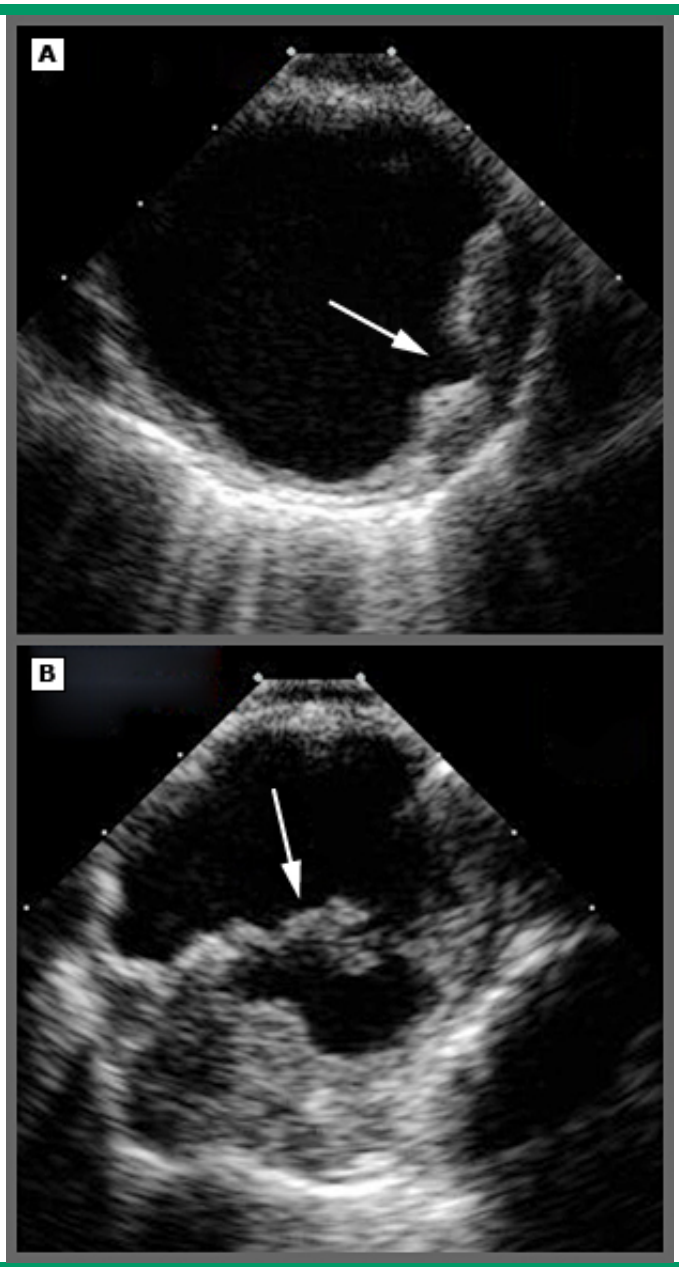
GRAPHICS

Autopsy specimen of atherosclerosis



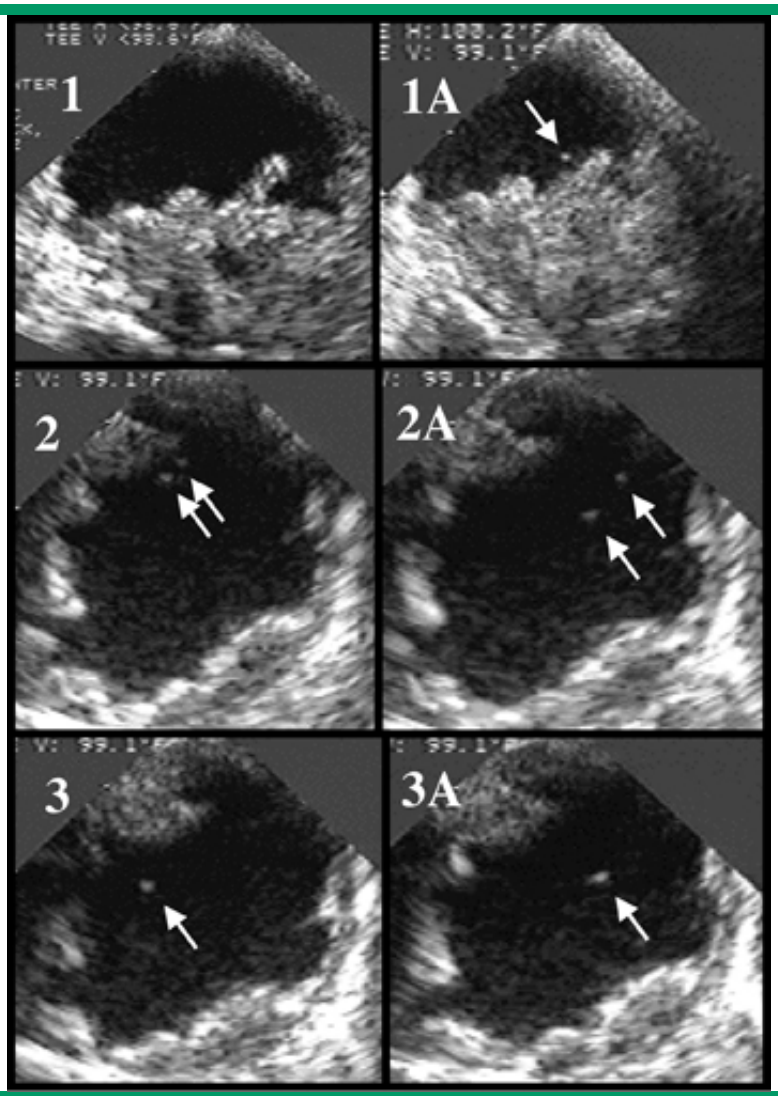
Autopsy specimen from a patient with cholesterol crystal embolism demonstrates severe atherosclerosis of the aorta.
Courtesy of Dr. Amy Rapkiewicz.

Complex atherosclerotic plaque in the thoracic aorta



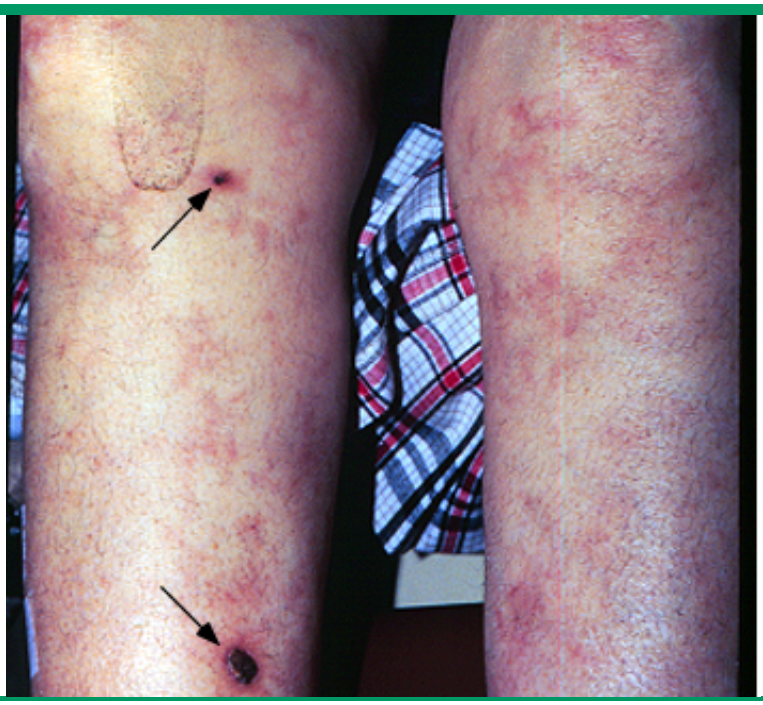
Complex atherosclerotic plaque in the thoracic aorta visualized by 2D TEE.
(A) Ulcerated plaque in the aortic arch.
(B) Plaque with a mobile component representing superimposed thrombus (arrow) in the descending thoracic aorta. *Courtesy of Dr. Muhamed Saric.*

Emboli in transit



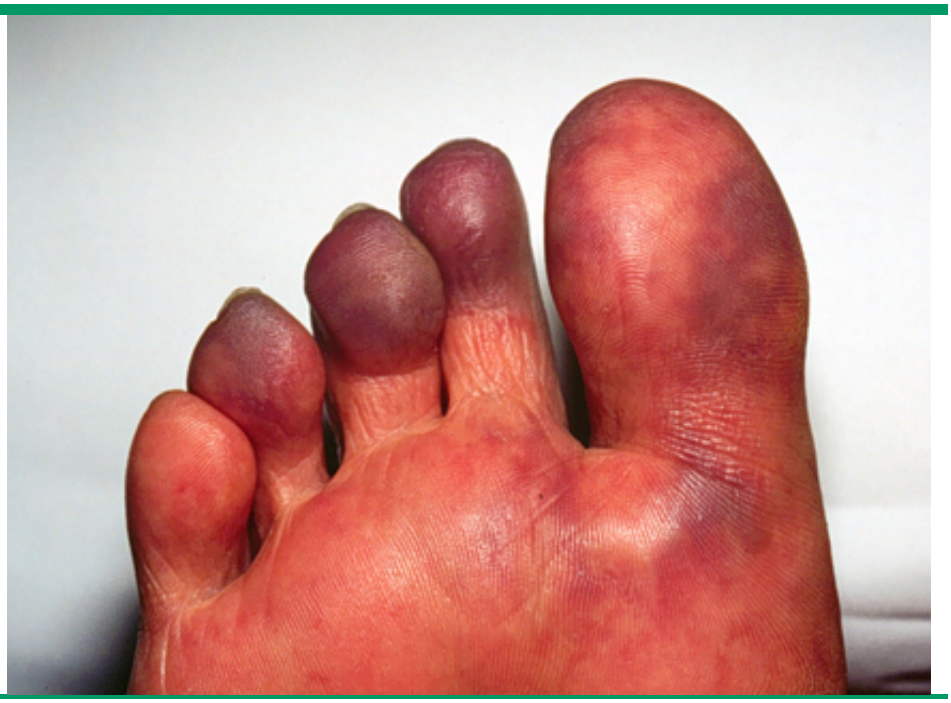
Transesophageal echocardiogram of the descending thoracic aorta in a patient who later died from cholesterol crystal embolization syndrome, with intestinal infarction and renal failure. Note the massive atherosclerotic plaque. The pictures on the right (1A, 2A, 3A) were taken one or two seconds after their respective pictures on the left. The arrows point to small particles of embolic material moving in transit in the aortic lumen. *Reproduced with permission from: Freedberg, RS, Tunick, PA, Kronzon, I. Emboli in Transit: The Missing Link. J Am Soc Echocardiogr 1998, 11:826. Copyright © 1998 Elsevier.*

Livedo reticularis



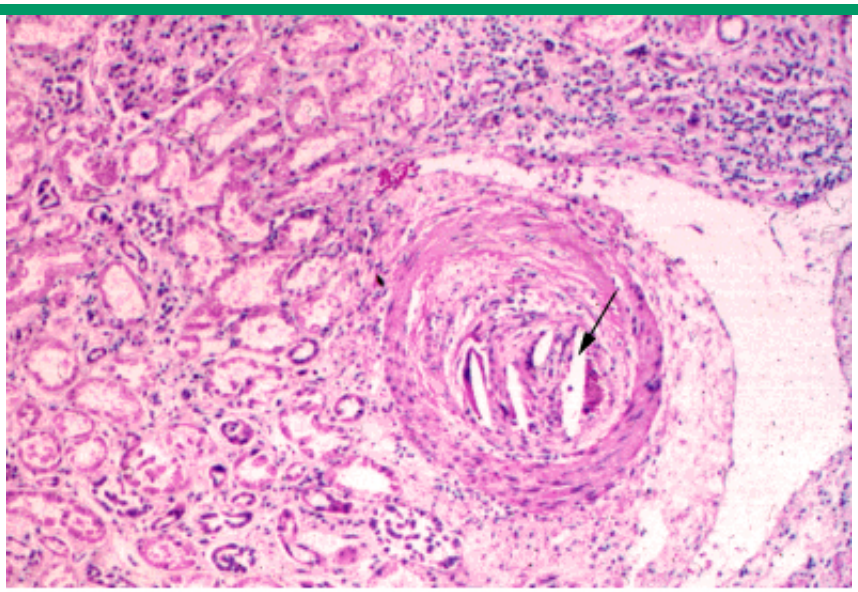
Patient with lupus and anti-phospholipid antibodies with livedo reticularis (manifested by a reddish-cyanotic, reticular pattern of the skin) which has resulted in ulcer formation (arrows).
Courtesy of Samuel Moschella, MD.

Blue toe syndrome



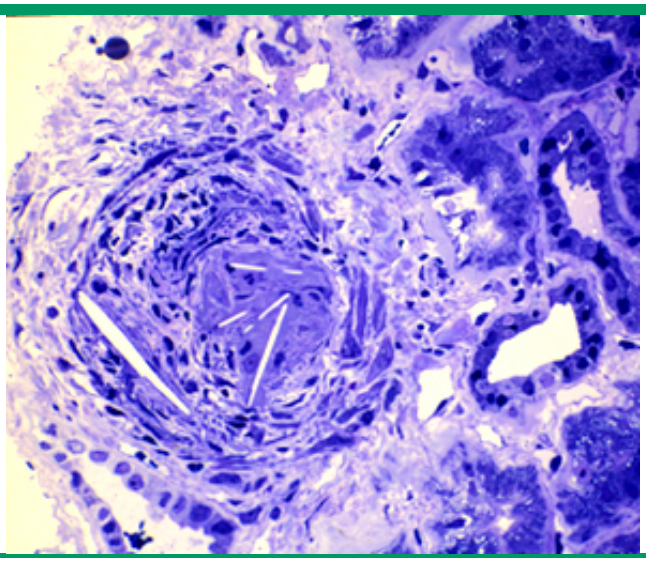
Blue toes are a classic manifestation of peripheral embolization of atheromatous material from proximal arterial sources (eg, aorta); the pedal pulses are often normal. This patient, who has a 30-year history of type 1 diabetes and severe peripheral vascular disease, presented with foot pain and discoloration. Cholesterol microemboli from the aorta were suspected to be the cause. *Reproduced with permission from Lawrence B Stack, MD. Copyright © Lawrence B Stack, MD.*

Renal atheroembolus



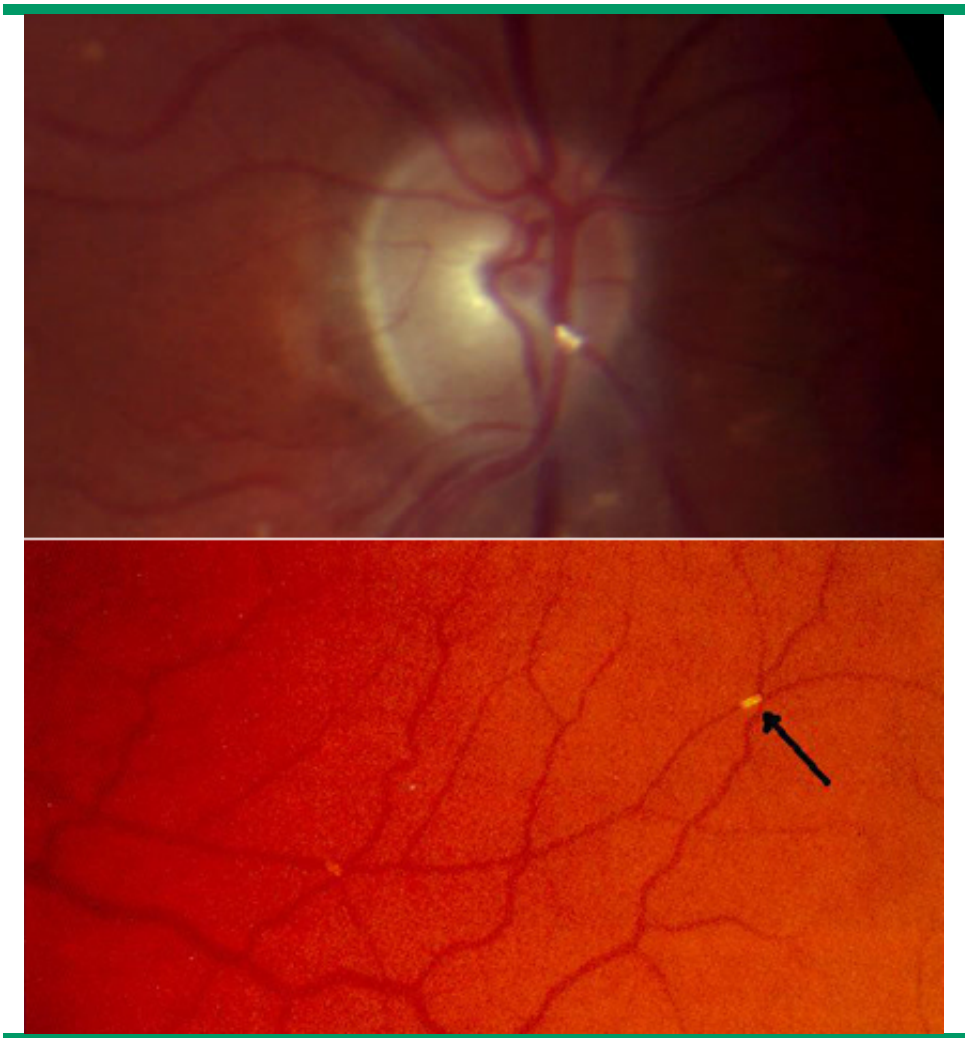
Light micrograph of an atheroembolus in a muscular renal artery showing cleft-like spaces (arrow) due to washout of the cholesterol crystals during histologic processing. *Courtesy of Helmut Rennke, MD.*

Renal atheroembolus



Thin section, toluidine blue stain shows the characteristic cholesterol clefts of an atheroembolus in the small renal artery.
Courtesy of Helmut Rennke, MD.

Hollenhorst plaque (cholesterol crystal, arrow) in retinal artery



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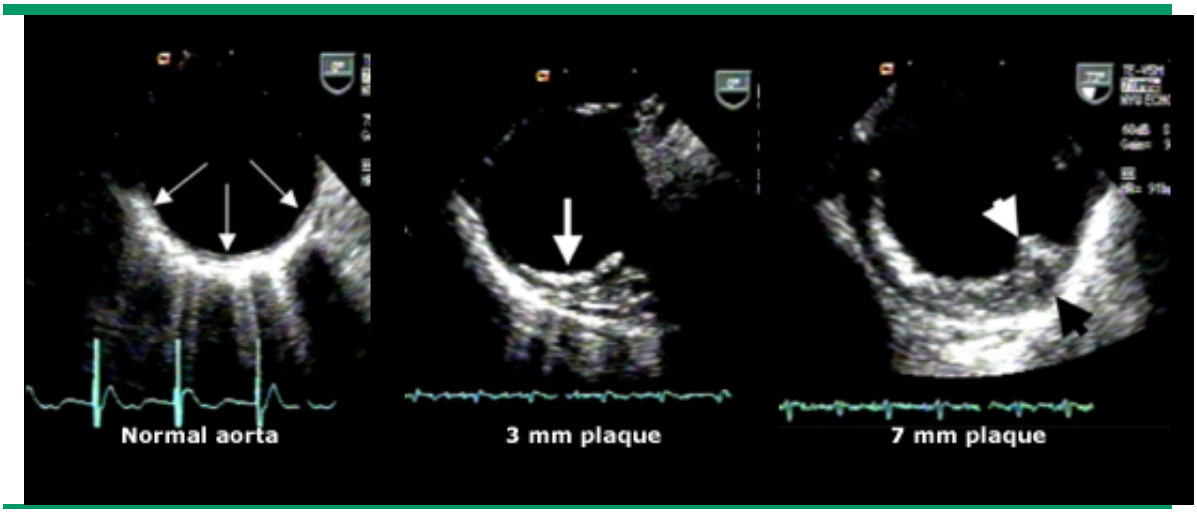
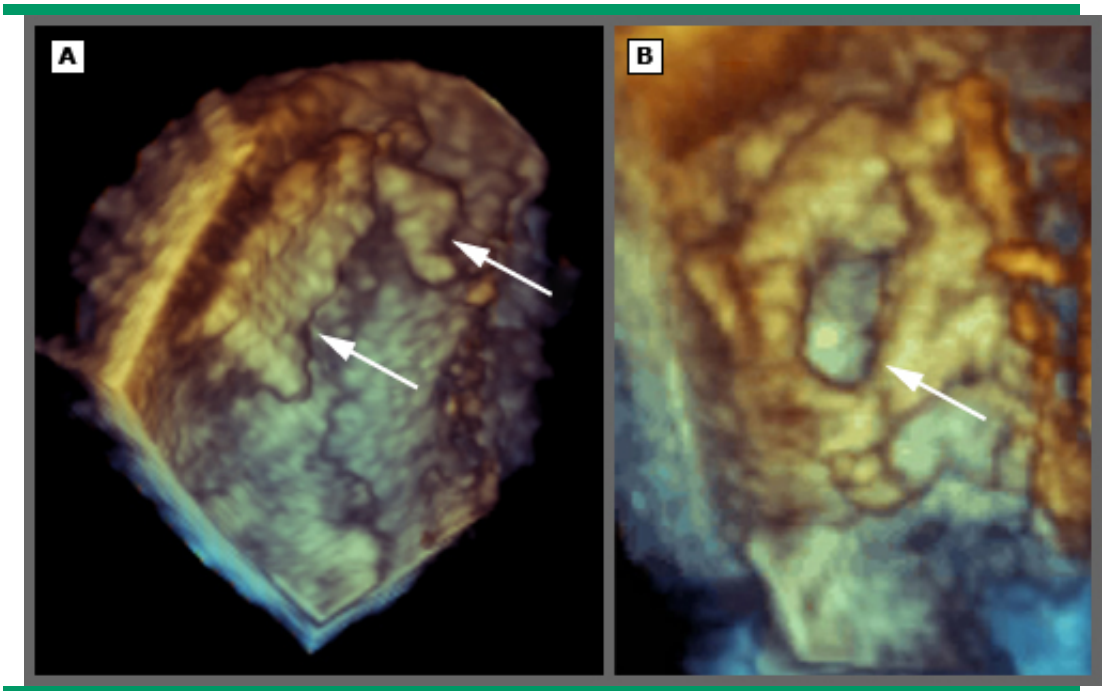
Thoracic aortic plaque



Three transesophageal echocardiograms of the thoracic aorta: left: normal; middle: moderate (3 mm) plaque; and right: severe (7 mm) plaque.

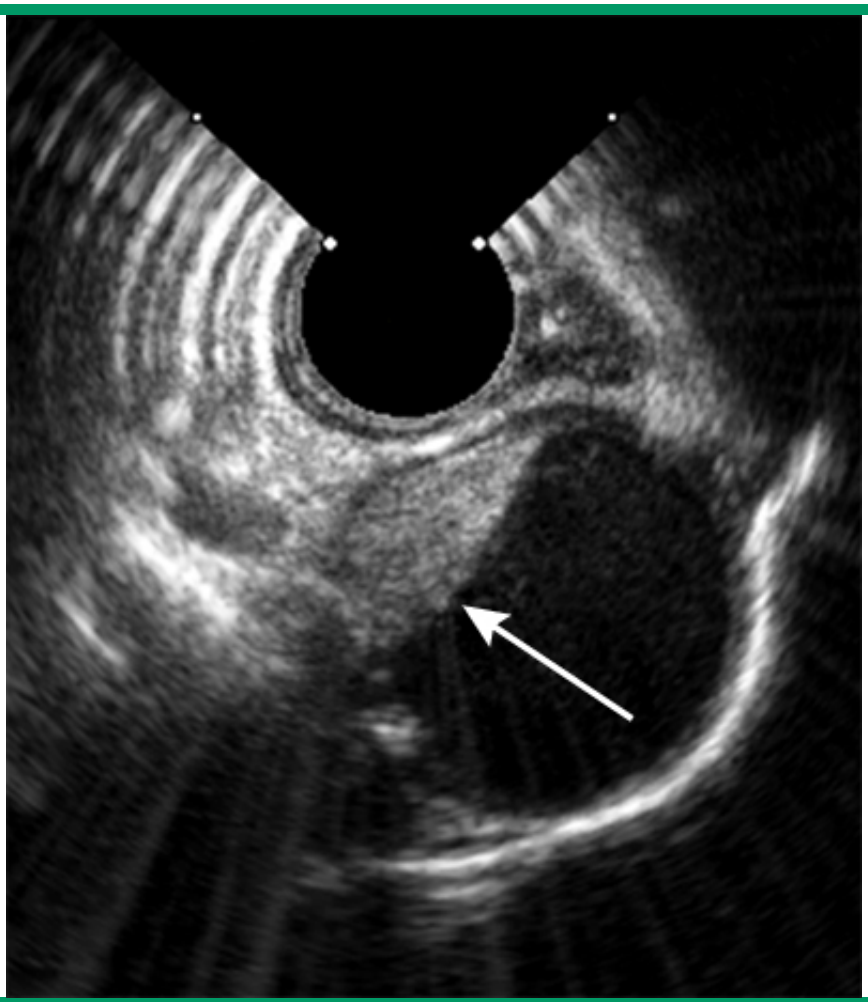
Reproduced with permission from: Tunick, PA, Kronzon, I. Atheroembolism. In: Vascular Medicine. A Companion to Braunwald's Heart Disease, 1st edition, Dzau, VJ, Creager, M, Loscalzo, J, et al (Eds), WB Saunders 2005. Copyright © 2005 Elsevier.

Atherosclerotic plaque visualized by 3D TEE



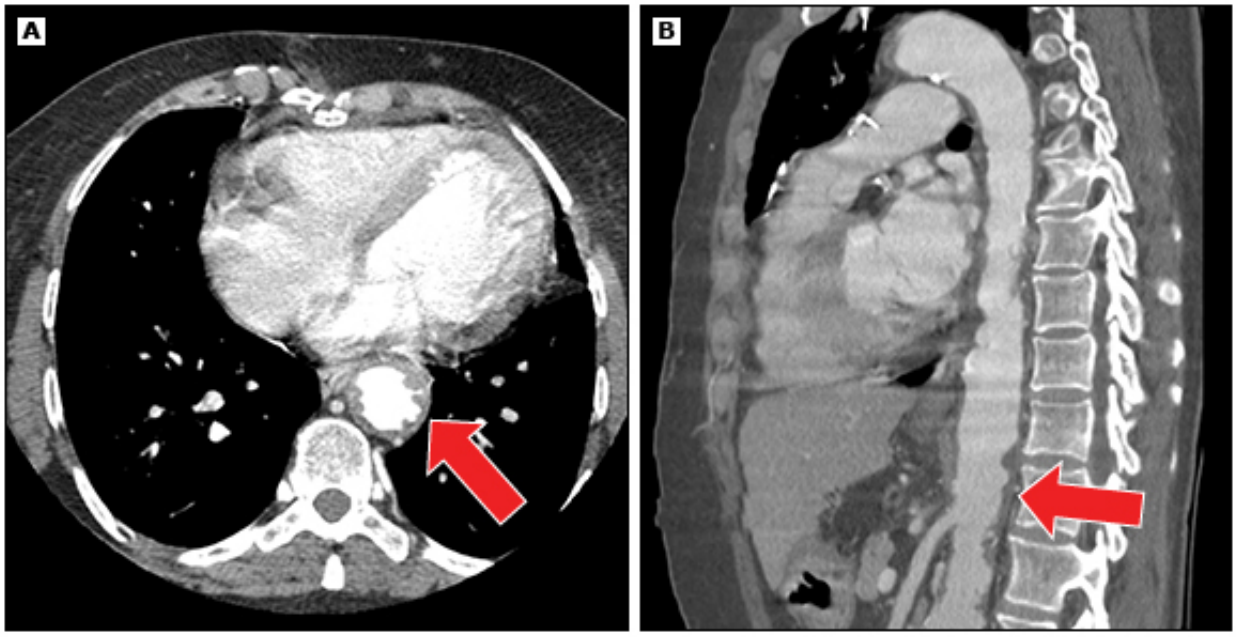
(A) Protruding plaque in the aortic arch.
(B) Ulcerated plaque in the descending thoracica aorta. *Courtesy of Dr. Muhamed Saric.*

Severe aortic plaque



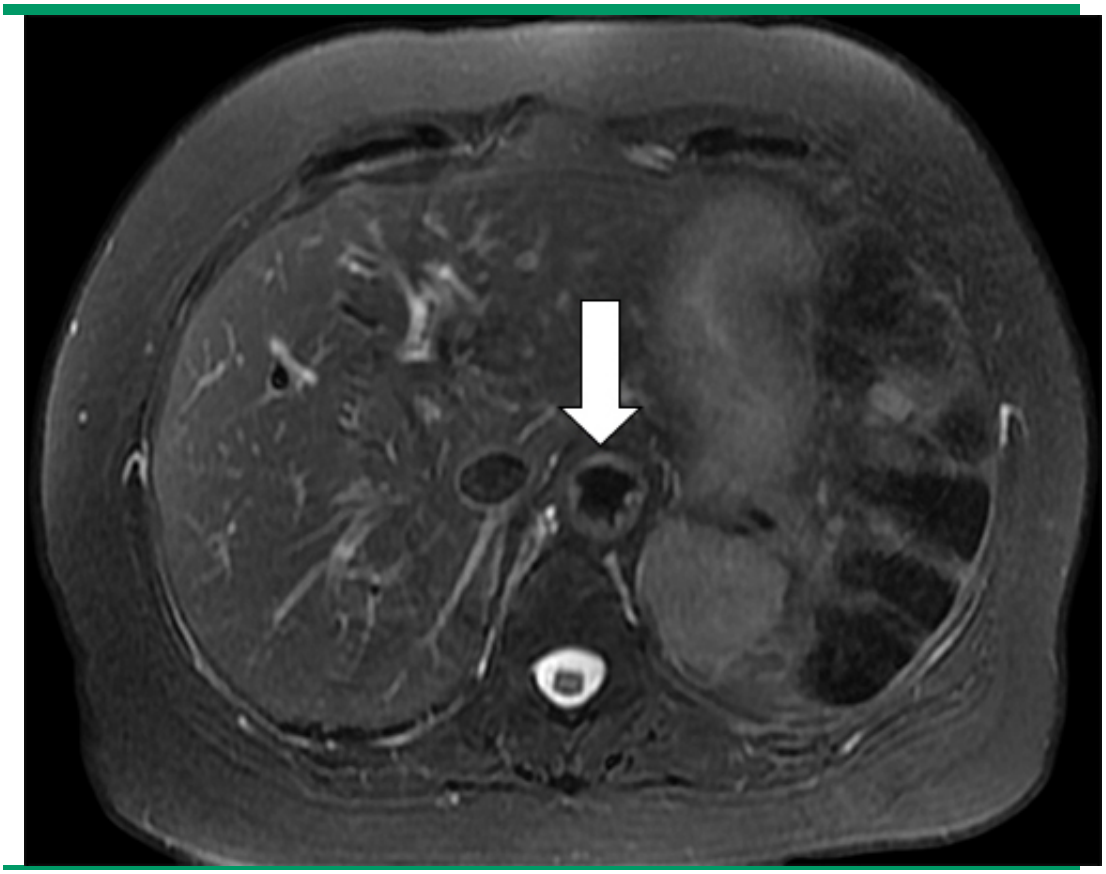
Severe aortic plaque (arrow) visualized by gastrointestinal endoscopic ultrasound (EUS) probe. *Courtesy of Dr. Zamir Brelvi, Division of Gastroenterology, New Jersey Medical School, Newark, NJ.*

Atherosclerotic plaque on CT



Atherosclerotic plaque of the descending thoracic and abdominal aorta on CT. Severe atherosclerotic plaque (arrows) visualized by CT in axial (panel A) and sagittal (panel B) projections. CT: computed tomography. *Courtesy of Dr. Pierre Maldjian.*

Aortic atherosclerosis on MRI



Aortic atherosclerosis (arrow) visualized by MRI (T2 weighted images with fat suppression). MRI: magnetic resonance imaging. *Courtesy of Dr. Pierre Maldjian.*