

Spectrum of Coronary Artery Aneurysms¹

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Abbreviations: ACAA = atherosclerotic coronary artery aneurysm, ADPKD = autosomal dominant polycystic kidney disease, CAA = coronary artery aneurysm, FOV = field of view, H-E = hematoxylin-eosin, LAD = left anterior descending coronary artery, MPR = multiplanar reconstruction, RCA = right coronary artery, TGF = transforming growth factor

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Advances in medical diagnosis reveal that coronary artery aneurysms (CAAs) may develop in several clinical scenarios and manifest variable symptoms, imaging appearances, and outcomes. Aneurysms are pathologically classified into three groups: atherosclerotic, inflammatory, and noninflammatory. The last category is associated with congenital, inherited, and connective tissue disorders. Overlap exists among the groups, because secondary atherosclerotic change may be present in an aneurysm of any cause. Atherosclerosis is the most common cause of CAAs in adults, and inflammation is considered the underlying mechanism. In children, Kawasaki disease is the most likely cause of CAAs. In both conditions, the aneurysms are usually multiple and affect more than one coronary artery. Mycotic (infectious), iatrogenic, and cocaine-induced CAAs are also well documented. Most CAAs are discovered incidentally, but potential cardiovascular complications include thrombosis, occlusion, fistula formation, rupture, myocardial infarction, and cardiac tamponade. Imaging modalities to evaluate a suspected CAA include transthoracic echocardiography, angiographic cardiac catheterization, electrocardiographically gated computed tomographic angiography, cardiac magnetic resonance (MR) imaging, and MR angiography. Management is usually individualized, and options include surveillance, anticoagulant therapy, percutaneous stent or coil placement, surgical resection, and coronary artery bypass grafting.

SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Recognize the most common causes of CAAs.
- Discuss the various types of vasculitides that can cause CAAs.
- Describe imaging appearances that may be helpful in determining the cause of a CAA.

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Introduction

The first published description of a coronary artery aneurysm (CAA) appeared in 1812, written by French physician Dr Charles Bougon. His patient was a male officer of the Hussars who “served during the Revolution,” “had yielded to all excesses,” and after returning home from military service suffered 4 years of nocturnal chest pain unresponsive to application of sternal leeches and administration of “large doses of cinchona.” The patient died at 40 years of age after an abrupt escalation of anginal symptoms; and at autopsy, Bougon found hemopericardium and a ruptured right coronary artery (RCA) aneurysm “into which the barrel of a goosequill could be easily introduced” (1). In 1929, the American Medical Association published the first review of CAAs (29 cases gathered from medical

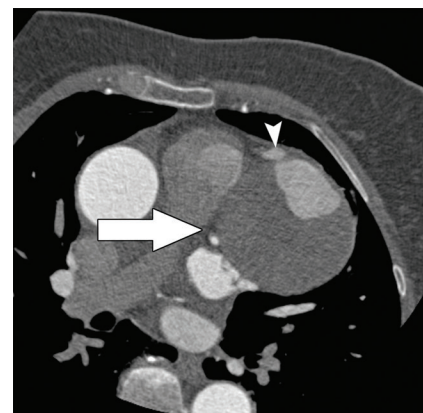
TEACHING POINTS

- The symptoms and complications of CCAs may be due to mass effect on adjacent cardiac structures, vasospasm, thrombosis, and/or embolism. Fistula formation occurs when vascular inflammation associated with the CAA causes erosion into adjacent cardiac structures. Critical consequences include myocardial ischemia or infarction, arterial rupture, and hemo-pericardium.
- CAAs are pathologically classified into three groups: atherosclerotic, inflammatory, and noninflammatory. In the last category, it is presumed that most noninflammatory CAAs are congenital or associated with connective tissue disorders. Overlap exists among the groups, because secondary atherosclerotic change may be found in an aneurysm of any cause, and inflammation in atherosclerosis is considered the underlying mechanism of aneurysm formation.
- Of all of the different causes of CAAs, atherosclerotic disease is the most common and accounts for at least 50% of CAAs diagnosed in adults.
- The most common vasculitis to cause acquired CAAs is Kawasaki disease, and 80% of these patients are younger than 5 years old. The etiology remains unknown but may be related to immune system maturation, possibly activated by an inhaled antigen. Clinical onset is acute and characterized by high fever, cervical lymphadenopathy, and mucocutaneous inflammation.
- TGF- β signaling is an established modulator of extracellular matrix structure and composition. Such mutations are believed to result in aneurysmal dilatation and dissection, most notably of the ascending aorta but also within the coronary arteries.

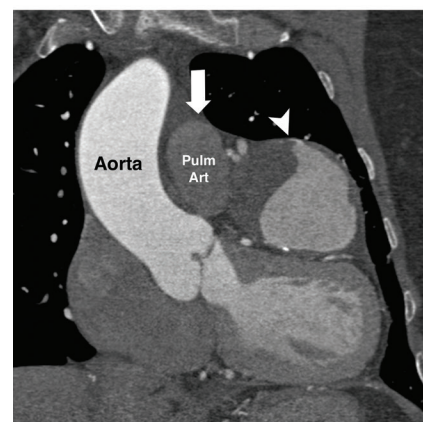
literature spanning the 19th century), and the investigators observed that CAAs can “vary in size from that of a pea to that of a pigeon’s egg” (2).

More than 2 centuries after Bougon’s first reported case, a CAA is now more precisely defined as a dilated vessel segment that measures at least 1.5 times larger in diameter than the diameters of the adjacent normal arterial segments (3). CAAs are often classified as saccular or fusiform. Atherosclerotic coronary artery aneurysms (ACAAs) are usually fusiform, whereas postinflammatory CAAs may be of either type. The term “*giant*” *aneurysm* is applied when the size exceeds 5 cm in diameter; these giant aneurysms are usually saccular (4,5) (Fig 1). Computer simulations of fluid dynamics within CAAs demonstrate complex flow variations showing mixed areas of stasis, turbulence, and recirculation, leading to an overall increased thrombotic risk (6).

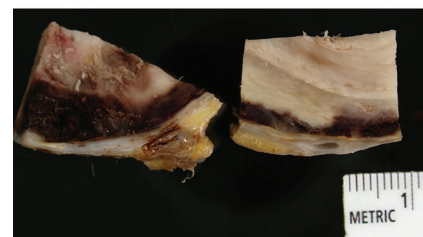
CAAs are often unsuspected and are typically discovered incidentally in the course of a diagnostic evaluation performed for other reasons. The mean incidence is quoted as 1.6% on the basis of autopsy and angiographic data, but the actual number of CAAs is unknown and is likely higher (3). In several studies, investigators have assessed CAAs in variable patient groups, and a few con-



a.



b.



c.

Figure 1. Isolated noninflammatory true aneurysm in a 68-year-old woman who presented with chest tightness after physical activity. (a, b) Axial (a) and coronal (b) computed tomographic (CT) angiographic images show a large, partially thrombosed mass (arrow) superior to the left ventricle and abutting the main pulmonary artery (*Pulm Art*). A branch of the left anterior descending coronary artery (LAD) (arrowhead) leads directly to the enhancing portion of the mass. (c) Photograph of sections of the gross specimen obtained at resection helps confirm the finding of a CAA with organized thrombus. (Scale is in centimeters.)

sistent observations have emerged: CAAs in adults are more common in male patients, the aneurysms are most often found in the setting of coronary artery atherosclerotic disease, and the presence of a CAA corresponds to a poorer clinical outcome than that in the general population (3).

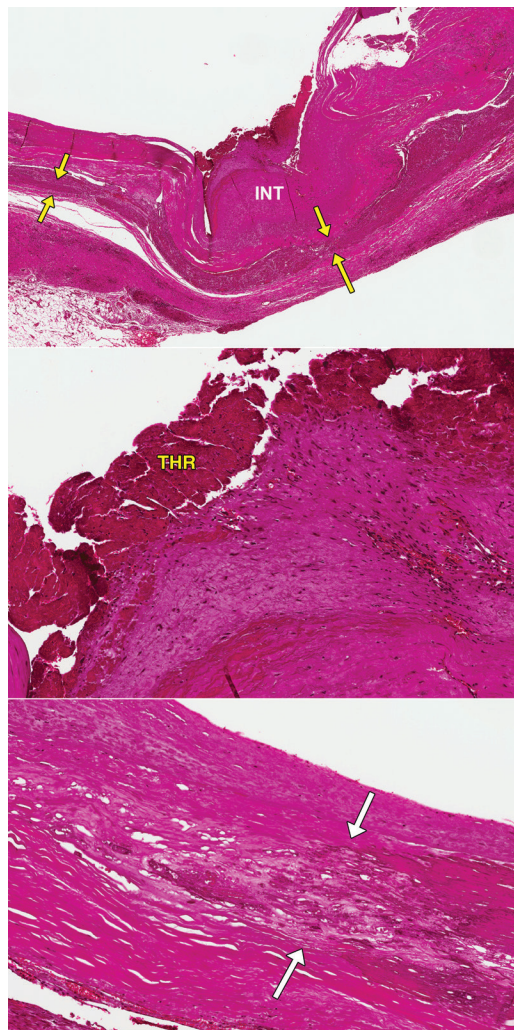


Figure 2. ACAA with nonspecific histopathologic findings. Top: Low-power photomicrograph of the surgical specimen shows thinning of the media (arrows). The intima (*INT*) is thickened with fibrous tissue. (Hematoxylin-eosin [H-E] stain; original magnification, $\times 40$.) Middle: High-power photomicrograph shows a surface thrombus (*THR*). (H-E stain; original magnification, $\times 100$.) Bottom: High-power photomicrograph shows an atherosclerotic lesion (arrows), a calcified fibroatheroma. (H-E stain; original magnification, $\times 100$.)

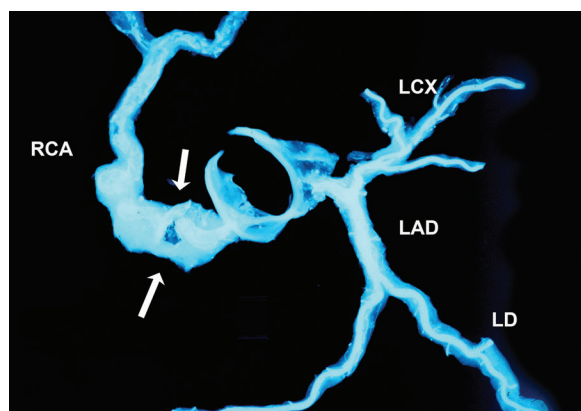
In adults, the most common predisposing condition for CAA is atherosclerotic coronary artery disease, a finding that supports a shared pathophysiology for the two conditions (7). In children, CAAs are typically multiple and associated with the systemic inflammation of Kawasaki disease. The range of reported incidences in the literature for congenital CAA is wide (1%–30%), and therefore, the true incidence remains uncertain. Immune-mediated factors and genetic susceptibilities are implicated in several diseases associated with CAAs, including systemic vasculitides and connective tissue disorders. Infections and iatrogenic events such as cardiac catheterization are also well-recognized but unusual causes.

The symptoms and complications of CAAs may be due to mass effect on adjacent cardiac structures, vasospasm, thrombosis, and/or embolism. Fistula formation occurs when vascular inflammation associated with the CAA causes erosion into adjacent cardiac structures. Critical consequences include myocardial ischemia or infarction, arterial rupture, and hemopericardium. In usual cases, a concomitant thoracic or abdominal aortic aneurysm is found, which may be clinically silent (8). Electrocardiographically gated CT angiography with the benefit of intravenous contrast material administration provides excellent characterization of CAAs, but a CAA may even be identified at chest radiography, transthoracic echocardiography, or magnetic resonance (MR) imaging. Depending on the clinical scenario and the imaging findings, a CAA may require medical management or more invasive procedures, including (a) the placement of percutaneous stent or coil devices or (b) coronary artery bypass surgery.

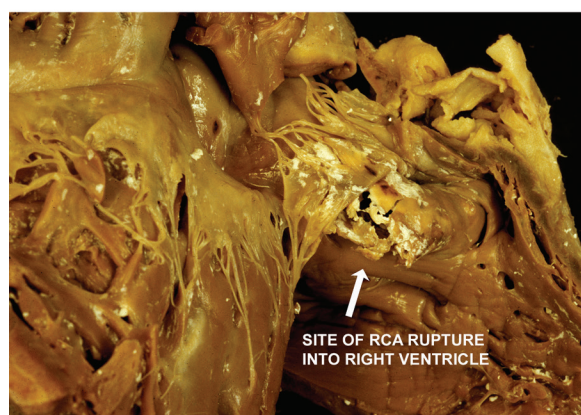
Pathophysiology of CAAs

CAAs are pathologically classified into three groups: atherosclerotic, inflammatory, and non-inflammatory. In the last category, it is presumed that most noninflammatory CAAs are congenital or associated with connective tissue disorders. Overlap exists among the groups, because secondary atherosclerotic change may be found in an aneurysm of any cause, and inflammation in atherosclerosis is considered the underlying mechanism of aneurysm formation. Unfortunately, the histopathologic characteristics of the aneurysm wall in CAAs have not been studied in detail, because CAAs are often treated percutaneously or with minimal excision of tissue. The findings from autopsy series provide the basis for much of our knowledge of the histopathologic characteristics of CAAs, and such series are heavily biased toward ACAAs.

In pathologic autopsy series, CAAs are highly represented by ACAAs, which account for 73%–90% of CAAs (7,9). The RCA and LAD are the most commonly affected coronary arteries, with the RCA being the most commonly affected, especially when the aneurysm is single. Between one-half and two-thirds of hearts with CAAs have multiple aneurysms. Almost all patients have severe atherosclerosis, with more than 75% luminal area narrowing of at least one epicardial artery. The CAAs themselves show atherosclerotic change with superimposed thrombosis. Medial thinning is a characteristic and is implicated in the pathogenesis of CAAs (7,9) (Fig 2). Rarely, destruction of the media may result in rupture (Fig 3). The fact that atherosclerosis is far more common than aneurysms has led to the theory that a second



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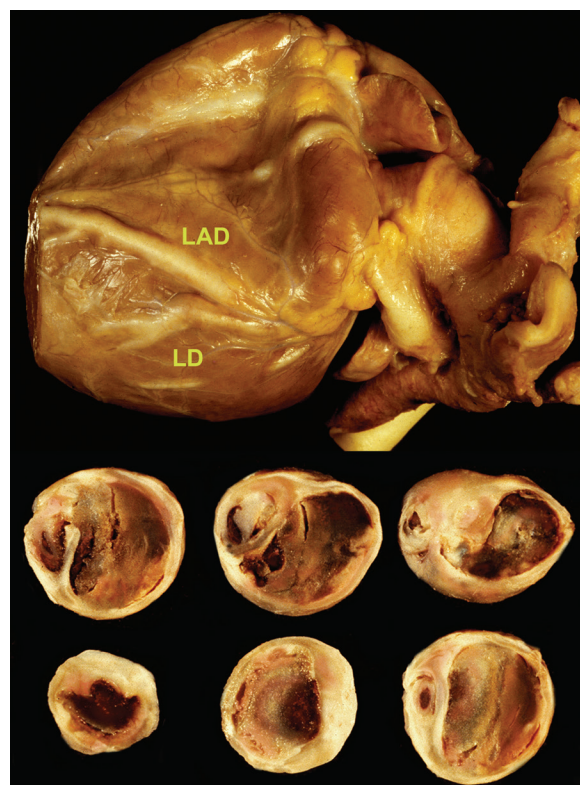


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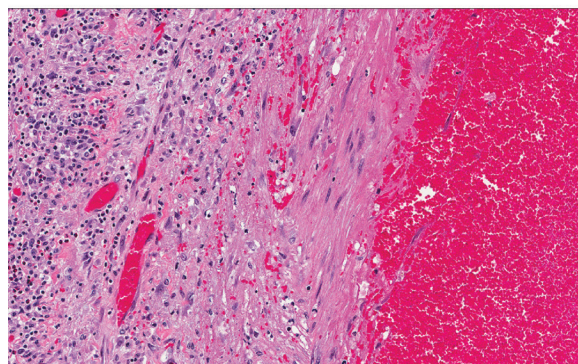
Figure 3. ACAA, with rupture into the right ventricle. (a) Post-mortem radiograph of a dissected vascular specimen obtained after injection of barium contrast material shows a disrupted aneurysm (arrows) in the proximal RCA. LCX = left circumflex coronary artery, LD = left diagonal artery. (b) Photograph of a gross specimen of the right ventricle obtained after postmortem injection of barium contrast material shows that extravasation of the contrast material (white material along the chordae of the tricuspid valve) has resulted from rupture of an aneurysm of the RCA into the right ventricle (arrow).

superimposed inflammatory process exists that results in aneurysms secondary to atherosclerosis (10). Atherosclerotic change can also be superimposed on inflammatory aneurysms, for example, those caused by Takayasu arteritis (11).

Inflammatory CAAs occur in much younger patients than ACAAs. Kawasaki disease is the cardiovascular manifestation of mucocutaneous lymph node syndrome and is the most common cause of CAAs in children. As with ACAAs, most hearts have multiple aneurysms. In the acute phase of Kawasaki disease, there is destruction of the media by acute and chronic inflammation with luminal thrombus, which may obstruct blood flow and result in ischemic symptoms (Fig 4). In the subacute phase, there is organization of the thrombus, with more fibrous intimal thickening and less inflammation. In young adults, the histopathologic findings of Kawasaki disease have been described in sudden death victims. The



a.



b.

Figure 4. Kawasaki disease in a 5-year-old boy. (a) Photograph shows a gross heart specimen (top) in the subacute phase that shows diffuse ectasia of the LAD and the left diagonal artery (LD). The two rows of cut specimens (bottom) show serial cross sections of a gross specimen of a thrombosed, dilated aneurysm. (b) Photomicrograph shows the artery wall, which is replaced by inflammation, with destruction of the media. The lumen is at the right (blood). (H-E stain; original magnification, $\times 100$.)

chronic histopathologic features are nonspecific and include stenoses, myofibroblastic intimal thickening, calcification, ossification, atherosclerosis, and recanalized thrombi. Medial thinning or complete destruction is always present (12).

A variety of other systemic inflammatory conditions have been associated with CAAs, including systemic lupus erythematosus (12–15), Behçet disease (16,17), ankylosing spondylitis (18), cardiac graft vasculopathy (19,20), granu-



Figure 5. Idiopathic aneurysm of the RCA. Photograph of the cut surface of the gross specimen shows white plastic probes indicating a normal coronary artery on either side of the aneurysm (in the center), which is filled with thrombus. The aneurysm wall is composed of fibrous tissue and thinned media without atherosclerotic change. (Scale is in centimeters.) (Courtesy of Joseph J. Maleszewski, MD, Mayo Clinic, Rochester, Minn.)

lomatosis with polyangiitis (21), eosinophilic granulomatosis with polyangiitis (22), Takayasu arteritis (11,23), immunoglobulin G4 (IgG4)–related disease (which more typically causes adventitial masses) (24), and hypergammaglobulinemia E (25). The histopathologic changes in these aneurysms have not been well documented but include acute inflammation with fibrinoid necrosis, thrombosis, and inflammatory destruction of the coronary arterial wall (7,12,20,26).

The etiology of noninflammatory nonatherosclerotic CAAs may be obscure (Fig 5) (27) or may be associated with connective tissue disorders such as Ehlers-Danlos syndrome (28,29) and Marfan syndrome (30,31). Patients with ascending aortic aneurysms associated with bicuspid aortic valve are more likely to have CAAs, although dedicated histopathologic studies have not been performed (32).

Two forms of aneurysms involving the coronary arteries are actually pseudoaneurysms: iatrogenic aneurysms and mycotic aneurysms. Both forms result from a defect in the media (traumatic or inflammatory, respectively) that results in extravasation of blood, along with a fibrous adventitial reaction that walls off the hemorrhage (4,5,33). Infectious (“mycotic”) aneurysms are associated with endocarditis and other conditions predisposing to bacteremia. Histopathologically, infectious aneurysms show acute inflammation and fibrin deposition, along with organisms, findings similar to those in infectious endocarditis.

Atherosclerotic Disease

Of all of the different causes of CAAs, atherosclerotic disease is the most common and accounts

for at least 50% of CAAs diagnosed in adults (34–37). Similar to coronary artery disease in general, men are more prone to develop ACAAs than women (35,37,38). Although the age range of patients with ACAAs varies widely among the results of various studies, most patients present in their 7th decade of life, notably older than those with congenital, noninflammatory, or inflammatory aneurysms (34,36,37,39,40). The exact incidence of ACAA is unknown, because many ACAAs are detected incidentally.

Risk factors for the development of ACAA are difficult to assess, because the findings in most articles do not distinguish between ACAA and other causes of CAAs. However, in the articles that do distinguish them, the development of ACAA tends to mirror the clinical factors related to coronary artery disease, which include male gender, hypertension, hyperlipidemia, and cigarette smoking (35,39–42). It is therefore not surprising that the presence of an ACAA is associated with areas of coronary artery stenosis. In the results of two clinical studies evaluating 31 patients with ACAAs, 22 patients (71%) had severe three-vessel disease, eight (26%) had severe two-vessel disease, and only one patient (3%) had severe single-vessel disease (Fig 6) (37,39). Autopsy findings of acute or healed myocardial infarction in 84%, and cardiomegaly in 78%, of those with ACAAs further support the coexistence of underlying coronary stenoses (7).

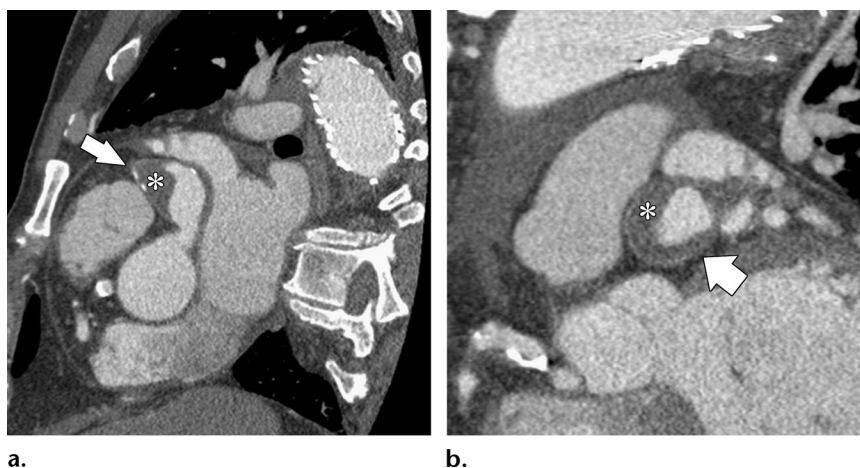
Electrocardiographically gated CT angiography is the best imaging modality for the depiction of ACAAs, because it allows complete evaluation of the aneurysm and any layering intraluminal thrombus, as well as coexisting coronary arterial plaque and overall vessel patency. Because cardiac catheterization provides only an endoluminal view, the true size of the aneurysm may be underestimated (Fig 7). The definitive diagnosis of ACAA requires histopathologic confirmation, but the specific diagnosis can be difficult to make on the basis of CT angiographic imaging alone, because CAAs of various causes often calcify with time. Other clues, such as the presence of multi-vessel disease in an older male patient, help to support the diagnosis. In addition, moderate to severe aortic atherosclerotic disease is present in most patients with ACAAs, and this observation further suggests atherosclerosis as the underlying cause of a CAA (7) (Fig 8).

Symptoms in patients with ACAAs vary and are primarily related to luminal patency (43). Lesions without stenosis tend to be asymptomatic even if the aneurysm itself is large (Fig 9). Debate exists about whether ACAA is an independent risk factor for death. In the results of one study in which an aneurysm was defined as more



Figure 6. ACAA in a 67-year-old man. (a) Left anterior oblique conventional angiographic image of the RCA shows a saccular aneurysm (arrow) of the RCA, as well as diffuse luminal irregularity (arrowheads) of the mid and distal portions of the RCA. (b) Axial CT angiographic image shows a focal outpouching (arrow) of the proximal RCA. (c) Coronal CT angiographic maximum intensity projection in the same projection as in a also shows a saccular aneurysm (arrowhead) of the proximal RCA.

Figure 7. ACAA in a 68-year-old man with unstable angina. Oblique sagittal (a) and oblique coronal (b) multiplanar reconstruction (MPR) CT angiographic images show fusiform dilatation of the LAD, with multifocal atherosclerotic plaque (arrow). Extensive mural thrombus (*) is depicted in the involved segments.



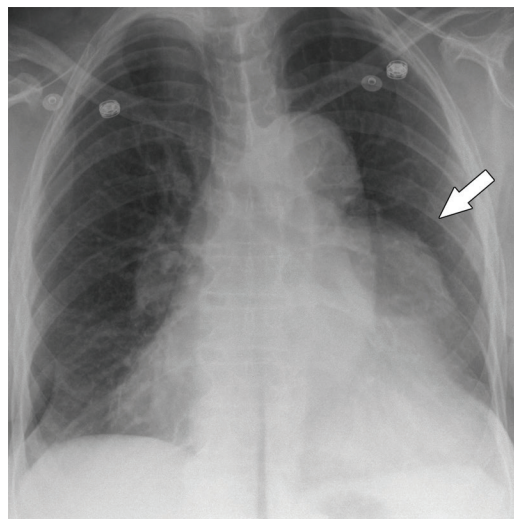
than 2 times the diameter of a normal adjacent segment, patients with ACAAs had a 56% higher mortality rate over 5 years than those without an aneurysm, even when investigators controlled for other clinical variables (41). In the findings from two large series assessing all patients with CAAs, not just those with ACAAs, the predicted 5-year mortality rate was similar, at 26% (44) and 29.1% (41). However, other investigators suggest that the prognosis of patients with coronary artery atherosclerotic disease without aneurysms is not significantly different from that of those with coronary artery atherosclerotic disease and ACAAs (10,42). Nonetheless, when a patient with an ACAA dies, in most cases the death is secondary to a cardiac event, including sudden cardiac death, acute myocardial infarction, or congestive heart failure (7).

Congenital CAA

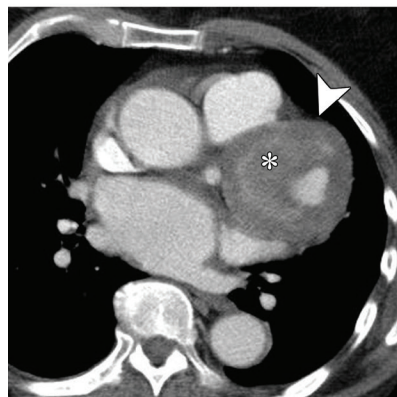
In early postmortem studies, investigators reported that 17% of CAAs were congenital in

origin, although in more recent articles, the range of incidence was broad, from less than 1% to 30% (3,36). In reality, it is often difficult to discern whether a CAA was present at birth or was acquired later as a result of infectious or inflammatory causes. Congenital CAAs, especially giant lesions, may be associated with other abnormalities, such as a coronary artery fistula (45). One hypothesis for the etiology of congenital CAAs is an inhibition in the normal development of coronary vessels, with retention of primitive sinusoids in the myocardium resulting in a blind-ending sac (46).

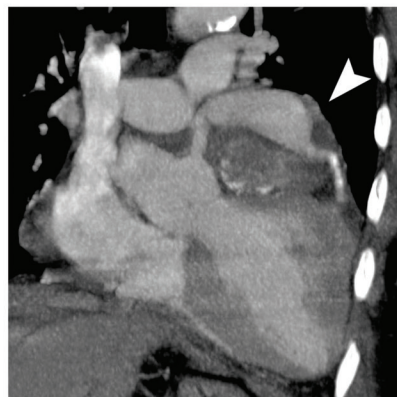
Although most patients remain asymptomatic, clinical manifestations vary from breathlessness to angina secondary to coronary luminal thrombosis. Imaging findings of congenital CAAs are similar to those of CAAs from other causes described previously. A chest radiograph may show cardiomegaly. Coronary CT angiography and conventional angiography may show a saccular aneurysm, with or without intraluminal thrombus. At MR imaging, cardiac functional images



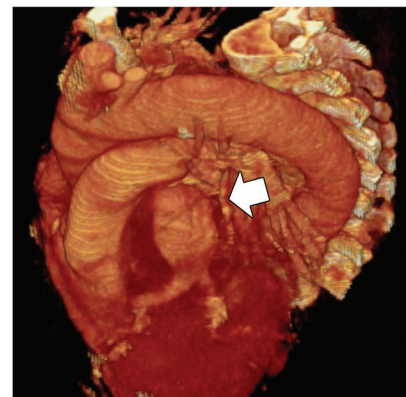
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Figure 8. ACAA in an 81-year-old man with hypertension who presented with acute back pain. (a) Frontal chest radiograph shows a contour abnormality of the left cardiac border (arrow). (b, c) Axial CT angiographic image (b) and coronal MPR image (c) show a giant aneurysm (arrowhead) of the proximal LAD. Note the zone of increased attenuation (*) on (b) in the periphery of the aneurysm, a finding suggestive of a more recent hemorrhage. (d) Three-dimensional volume-rendered CT angiographic image further shows the anatomic relationship between the LAD aneurysm and regional structures (arrow). The results of a subsequent cardiac catheterization helped confirm a giant, partly thrombosed coronary aneurysm.

may demonstrate a wall motion abnormality if ischemia is present. Complications of congenital CAAs include myocardial infarction, coronary artery rupture, and, rarely, sudden death (Fig 10).

Vasculitis

Kawasaki Disease

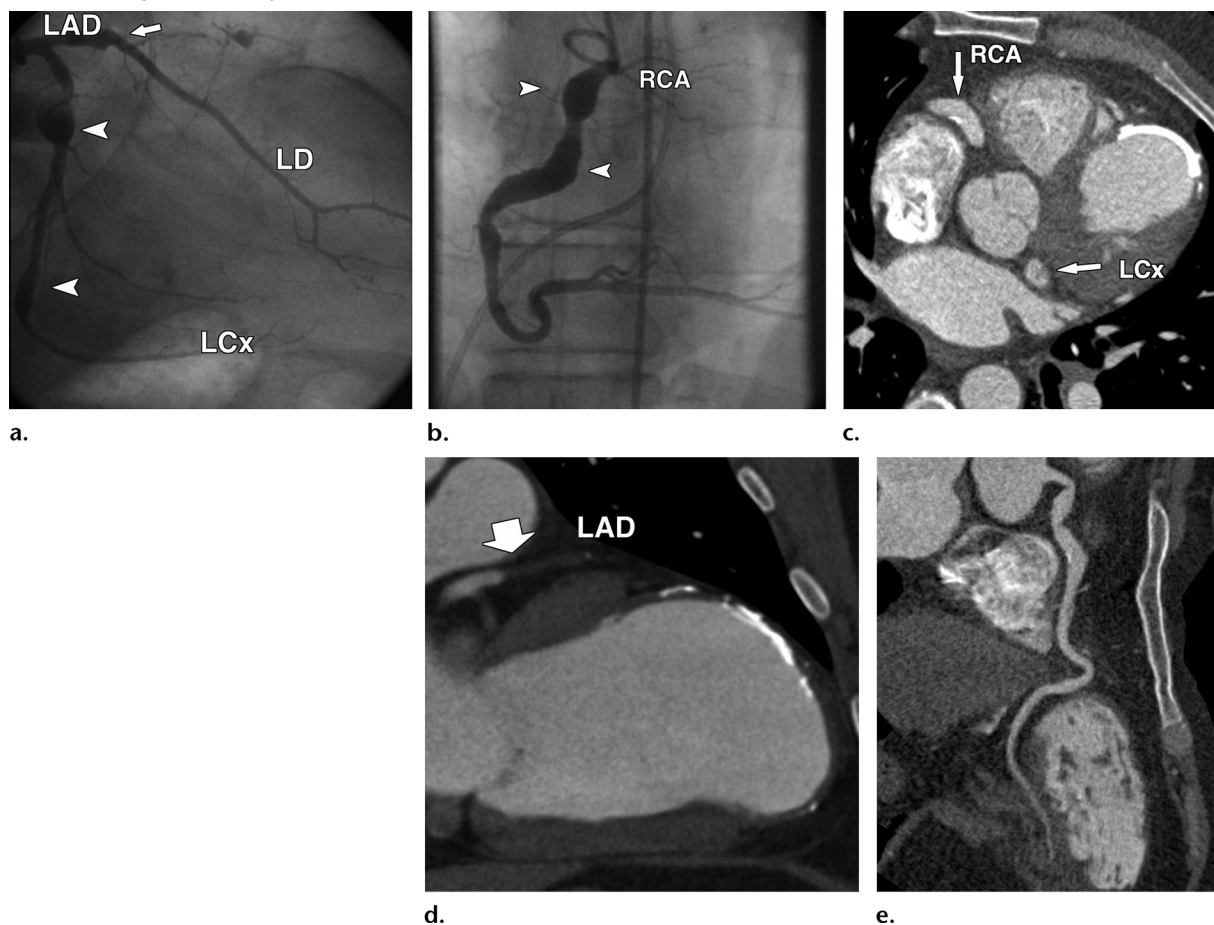
The most common vasculitis to cause acquired CAAs is Kawasaki disease, and 80% of these patients are younger than 5 years old. The etiology remains unknown but may be related to immune system maturation, possibly activated by an inhaled antigen. Clinical onset is acute and characterized by high fever, cervical lymphadenopathy, and mucocutaneous inflammation. Diagnosis is made according to the American Heart Association/American Academy of Pediatrics criteria (47). Kawasaki disease was first described by Tomisaku Kawasaki in 1967 in Japan, the country with the greatest incidence of Kawasaki disease, with 265 cases per 100 000 children younger than 5 years old (48). The United States has a lower incidence of 19 cases per 100 000 children younger than 5 years old. Within the United States, the state of

California has the greatest incidence, at 24.7 per 100 000 children younger than 5 years old (49).

CAAs develop in 15%–25% of children who are not treated with intravenous immunoglobulin therapy during the febrile phase of Kawasaki disease. Even with treatment, 5%–10% of patients will form a CAA (47,50,51) (Fig 11). Absence of administration of intravenous immunoglobulin therapy in patients with acute Kawasaki disease is even considered an independent risk factor for a major adverse cardiac event later in life, likely owing to aggressive inflammatory changes in the coronary arteries during the acute phase of the disease (52). Aneurysms are usually detected within 10–14 days after the onset of illness and may enlarge if refractory to treatment (51). The proximal LAD and proximal RCA are the vessels most frequently affected, followed by the left main coronary artery, the left circumflex coronary artery, and the distal RCA (47).

Noninvasive cardiac imaging plays an important role in the evaluation of patients with definite or suspected Kawasaki disease. During the acute phase of illness, echocardiography is performed to evaluate coronary artery morphologic structure,

Figure 9. Multiple ACAAs in a 52-year-old man. (a, b) Right anterior oblique conventional angiographic image obtained after injection of the left main coronary artery (a) and left anterior oblique conventional angiographic image obtained after injection of the RCA (b) show aneurysms of the proximal left circumflex coronary artery (LCx) (arrowheads on a) and the RCA (arrowheads on b). The proximal LAD is occluded (arrow on a) just beyond its bifurcation from the left main coronary artery. LD = left diagonal artery. (c) Axial CT angiographic image shows dilatation (arrows) of the proximal RCA and the proximal left circumflex coronary artery (LCx). (d) MPR CT angiographic image obtained in the vertical long axis shows the occluded LAD (arrow) and ventricular remodeling of the anterior wall and ventricular apex from a prior myocardial infarct. (e) Curved planar reformatted CT angiographic image of the RCA shows focal regions of aneurysmal involvement and subtle eccentric calcification.



as well as left ventricular and valvular function; coronary thrombi may be detected. The initial measurements of the CAA provide important risk stratification data and are regarded as strongly predictive of CAA persistence and future adverse cardiac events (52). Protocol requires detailed segmental coronary anatomic views for baseline and follow-up serial evaluations. Measurements of the internal diameter of proximal coronary artery segments are normalized for body surface area and assigned a z score, which reflects standard deviation units from the mean (50). With a z score of 10 or more or a CAA size of 8 mm or more (fulfilling the pediatric definition of a giant CAA), anticoagulant therapy is indicated (Fig 12). The size definition of a giant CAA in a young pediatric patient is generally accepted as larger than 8 mm in diameter, compared to the size definition for an adult giant CAA of larger than 5 cm in diameter. Serial echocardiography is performed until coronary measurements stabilize (50).

Long-term imaging surveillance is indicated for patients with z scores of 2.5 or more or those with a giant CAA. These criteria assist in the risk stratification of patients who are more likely to suffer future cardiac events and thus require closer surveillance or more aggressive treatment (Fig 13). As the child grows, the modalities used to assess the heart and coronary arteries include transesophageal echocardiography, conventional catheter-based angiography, nuclear medicine stress perfusion imaging, MR imaging, and electrocardiographically gated CT angiography. Imaging is tailored to assess for aneurysm expansion, thrombosis, calcification, vascular stenosis, occlusion, and myocardial ischemia or infarction (50).

Coronary CT angiography is a sensitive noninvasive test to evaluate older patients for Kawasaki disease-associated coronary abnormalities (Fig 14). Interestingly, low-attenuation lesions that mimic noncalcified atherosclerotic plaque may also

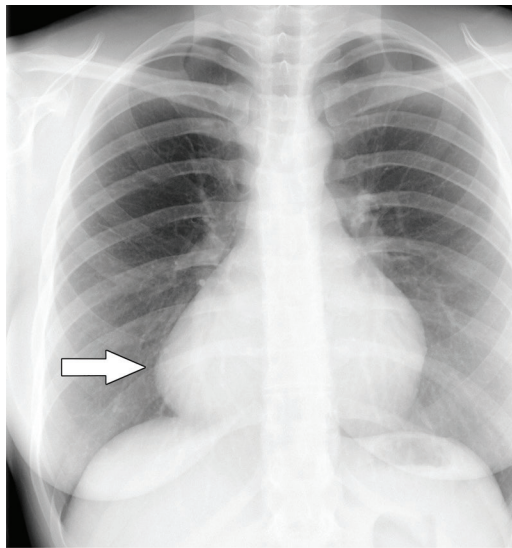
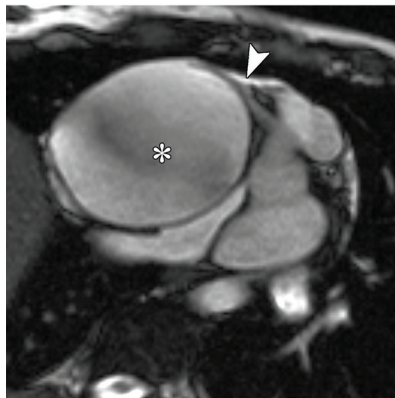
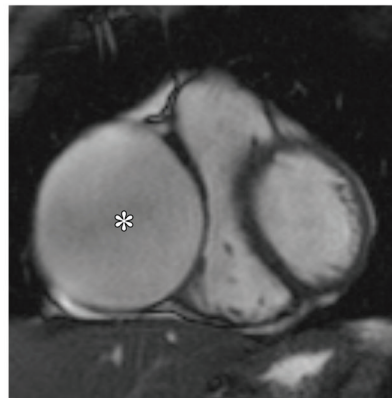


Figure 10. Congenital or idiopathic CAA in a 26-year-old woman who presented with dysarthria and right upper extremity weakness. At MR imaging, a subacute cerebral infarct was demonstrated, a finding that prompted a search for an embolic source. **(a)** Posteroanterior chest radiograph shows a contour abnormality of the right cardiac border (arrow). **(b, c)** Short-axis **(b)** and right ventricular outflow tract **(c)** steady-state free precession MR images (30.3/1.47 [repetition time msec/echo time msec]; 70° flip angle; field of view [FOV], 360 × 360) show a large hyperintense epicardial mass (*) compressing the right atrium and right ventricle. The RCA courses just anterior to the mass (arrowhead in **b**). **(d)** Intraoperative photograph shows a large aneurysm of the RCA; a fistulous connection to the right atrium (arrowhead) was found at surgery. In addition, the patient had a patent foramen ovale, which presumably facilitated paradoxical embolism from the coronary aneurysm. RV = right ventricle. (Upper scale is in centimeters; lower scale is in inches.)

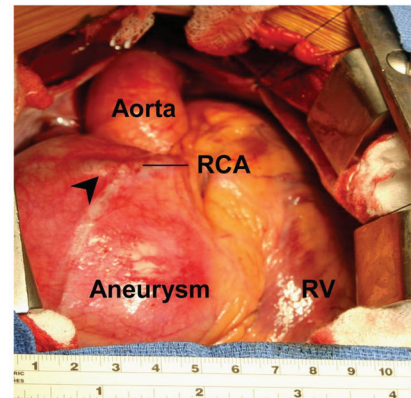
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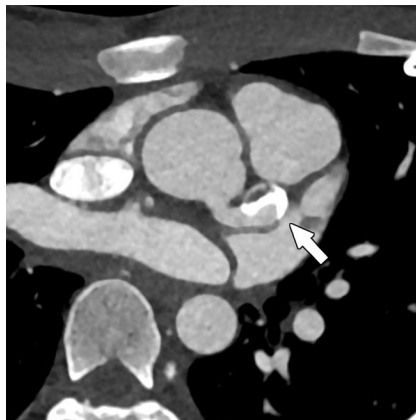
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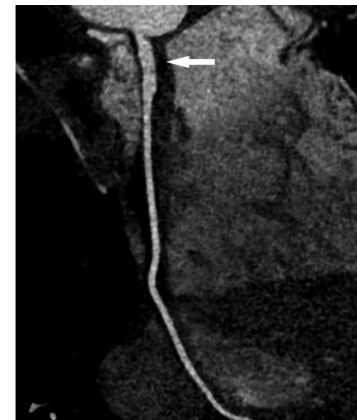
d.



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Figure 11. Kawasaki disease. **(a)** Oblique axial CT angiographic image shows a CAA (arrow) with eccentric thrombus and a partly calcified rim in the proximal LAD. **(b)** MPR CT angiographic image shows a partly calcified aneurysm with eccentric thrombus (arrowhead) in the proximal left circumflex coronary artery. **(c)** MPR CT angiographic image shows ectasia (arrow) of the proximal RCA.

be observed (53). The coarse calcifications often described within the coronary arteries of patients with Kawasaki disease is a later finding, usually evident years after the acute phase and rarely seen without underlying CAAs (53) (Fig 15). In

patients with a remote history of Kawasaki disease (>9 years after the acute phase), low-dose CT coronary artery calcium scoring has been piloted as a screening tool for the detection of CAAs and may prompt a search for underlying myocardial

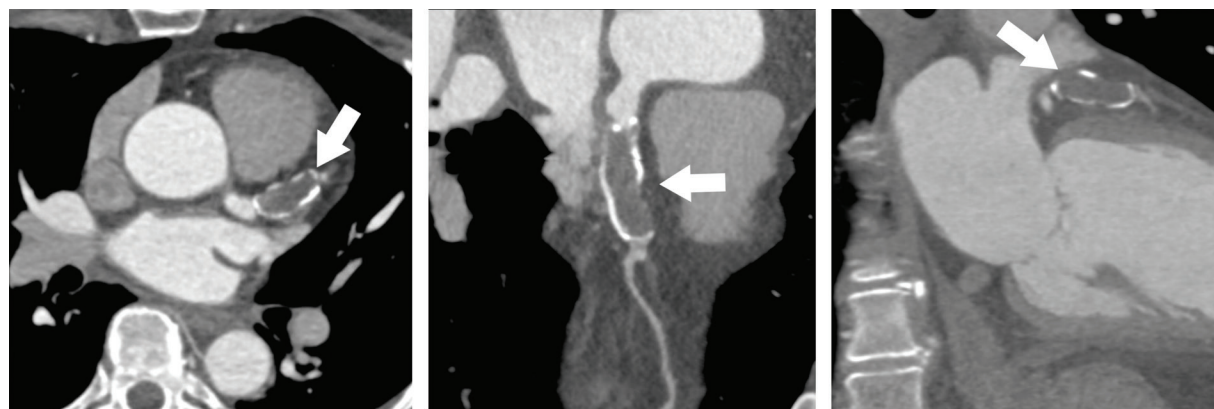


Figure 12. Kawasaki disease. (a–c) Axial (a), MPR (b), and vertical long-axis (c) CT angiographic images show rim calcification and complete occlusion of a CAA (arrow) in the proximal LAD. (d) Volume-rendered CT angiographic image shows the surface anatomy of the proximal LAD aneurysm (arrowhead).

ischemia or an impending cardiac event (53). Myocardial infarction is the most important determinant of long-term outcome in patients with Kawasaki disease who have a giant CAA (54). Kawasaki disease should remain prominent in the differential diagnosis of a CAA with rim calcification identified in adulthood because of the prevalence of this disease, particularly in the absence of advanced coronary atherosclerosis (55).

In the United States, the results of the largest cohort study to date of patients with Kawasaki disease who have a CAA showed an overall CAA regression rate of 75% within 2 years (52). Although “regression” may reflect a return to normal luminal diameter, it does not always correlate with restored arterial wall architecture; these arteries may still be at risk for future events (52) (Fig 16). In the results of this study, major adverse cardiac events occurred in 6% of U.S. patients with Kawasaki disease who were treated with intravenous immunoglobulin (IVIG) therapy; these events arose exclusively in cases complicated by a giant CAA (52). In the group of patients with Kawasaki disease who did not receive IVIG therapy, 25% experienced major adverse cardiac events. Myocardial ischemia, myocardial infarction, and sudden death may occur because of an aneurysm sac thrombosis with acute occlusion, embolism, rupture, and/or cardiac infarction (51) (Fig 17).

Behçet Disease

Behçet disease is a chronic, relapsing systemic vasculitis of unknown etiology that can affect virtually any organ or mucosal layer in the body. Behçet disease involves veins (29%) more commonly than arteries (8%–18%), affects vessels of all sizes, and causes vascular aneurysms, stenosis, and thrombosis (56). The classic manifestation includes



d.

recurrent genital ulcers, aphthous stomatitis, skin lesions, including erythema nodosum, and ocular findings (uveitis or iridocyclitis). The disease tends to manifest in young adults and most commonly affects men in the 3rd and 4th decades of life. Although there is a probable genetic susceptibility related to the major histocompatibility complex HLA-B51/B5 allele, an environmental or infectious agent may actually incite the strong immunologic response (57,58).

The moniker “Silk Road disease” was given to Behçet disease because it often occurs in patients whose ancestry traces to settlements along this ancient commercial trade route spanning East Asia to the Mediterranean basin. The disease is most prevalent in Turkey (80–420 cases per 100 000 persons), where it was first described in 1937 by Dr Hülûsi Behçet, a dermatologist and specialist in venereal diseases. In the United States, the rate of occurrence of Behçet disease is 0.38/100 000 (57,59). Inflammatory changes centered on the heart include pericarditis, endocarditis, myocarditis, valvular disease, intracardiac thrombus, and coronary vasculitis (56). Cardiac involvement is variably reported

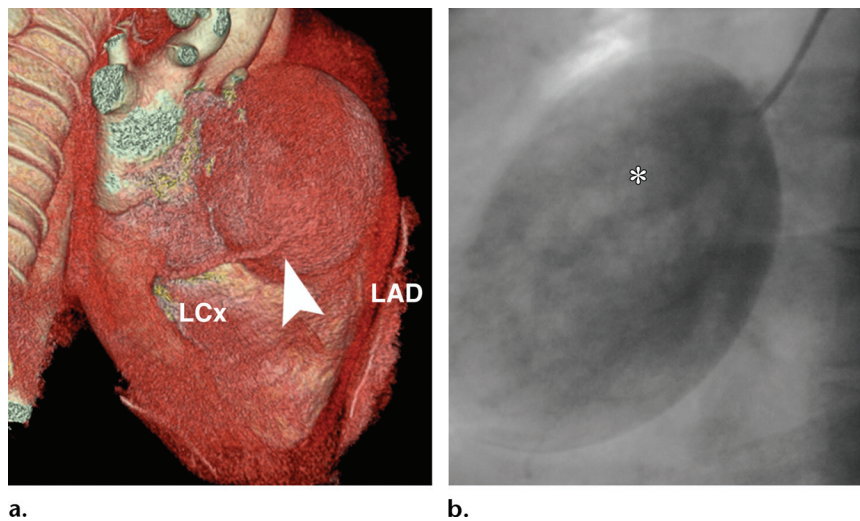


Figure 13. Kawasaki disease in an asymptomatic 28-year-old patient. (a) Three-dimensional volumetric CT angiographic image shows a large aneurysm (arrowhead) at the juncture of the LAD and the left circumflex coronary artery (LCx). (b) Left anterior oblique magnified and collimated angiographic image obtained after cardiac catheterization with select injection of the left circumflex coronary artery shows the aneurysm (*), with no angiographic evidence of thrombosis within the aneurysm.

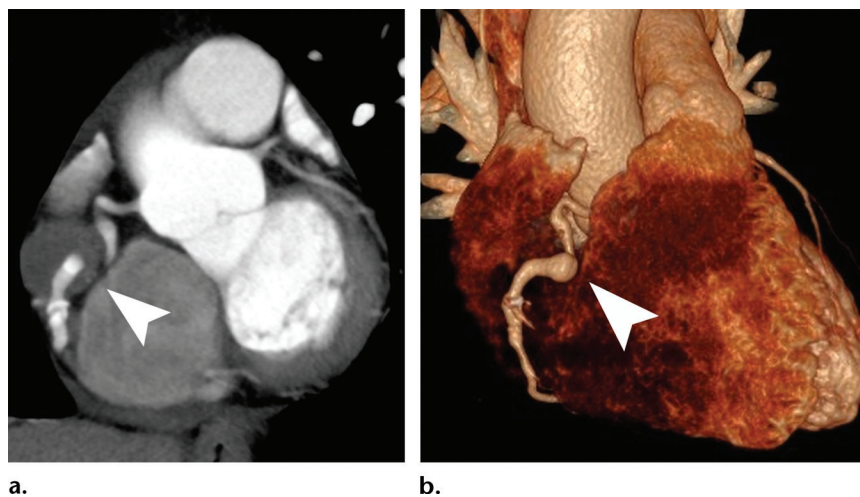


Figure 14. Kawasaki disease. Oblique sagittal thick MPR (a) and volume-rendered (b) CT angiographic images show a partly thrombosed aneurysm (arrowhead) in the RCA.

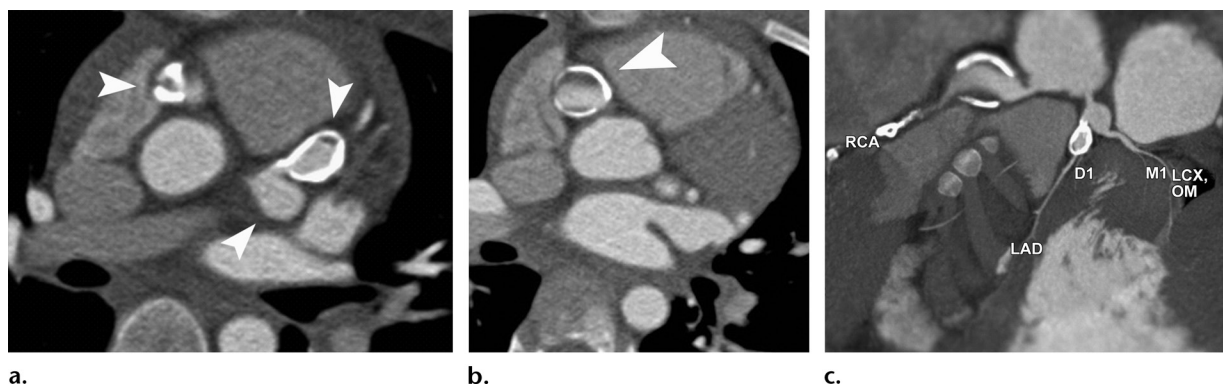


Figure 15. Kawasaki disease. (a, b) Axial CT angiographic images (b obtained just inferior to a) highlighting the aneurysm in the LAD (a) and the aneurysm in the RCA (b) show multiple rim-calcified aneurysms with eccentric thrombus (arrowheads). (c) Spider MPR CT angiographic image shows a global view of multiple aneurysms within all three coronary arteries. D1 = first diagonal branch, LCX = left circumflex coronary artery, M1 = first obtuse marginal branch; OM = obtuse marginal branch.

to occur in 7%–46% of patients; coronary artery involvement is reported in 1%, with aneurysms, thrombosis, and occasionally rupture (56,60). The manifestations of a CAA in patients with Behçet disease range from no symptoms to acute coronary syndrome.

Imaging modalities used to investigate Behçet disease include echocardiography, CT angiography, and MR imaging. Dedicated coronary imaging may depict stenosis, saccular aneurysms involving one or more coronary arteries, and areas of eccentric intraluminal thrombus (60–65).

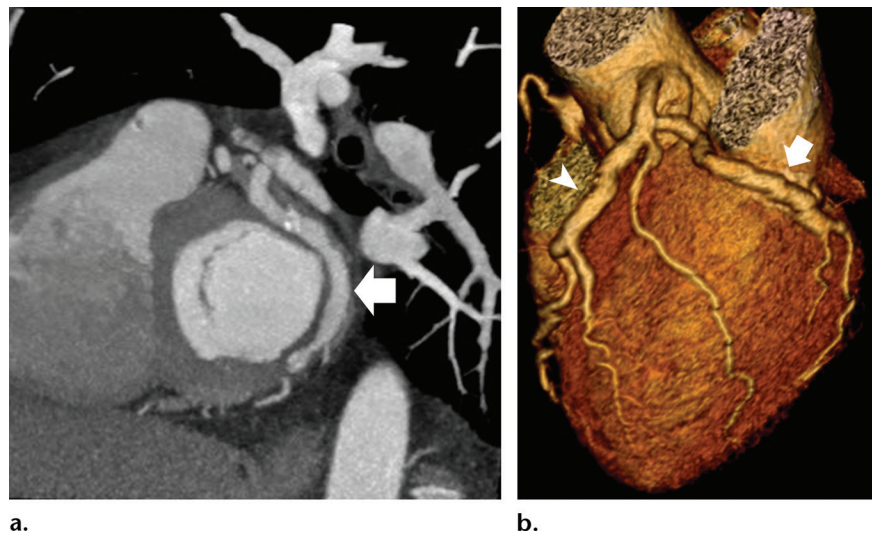


Figure 16. Kawasaki disease in a 28-year-old patient. Oblique sagittal MPR (a) and three-dimensional volume-rendered (b) CT angiographic images show ectasia of the left circumflex coronary artery (arrow) and the LAD (arrowhead on b). The patient had minimal atherosclerotic disease and no focal coronary artery luminal narrowing.

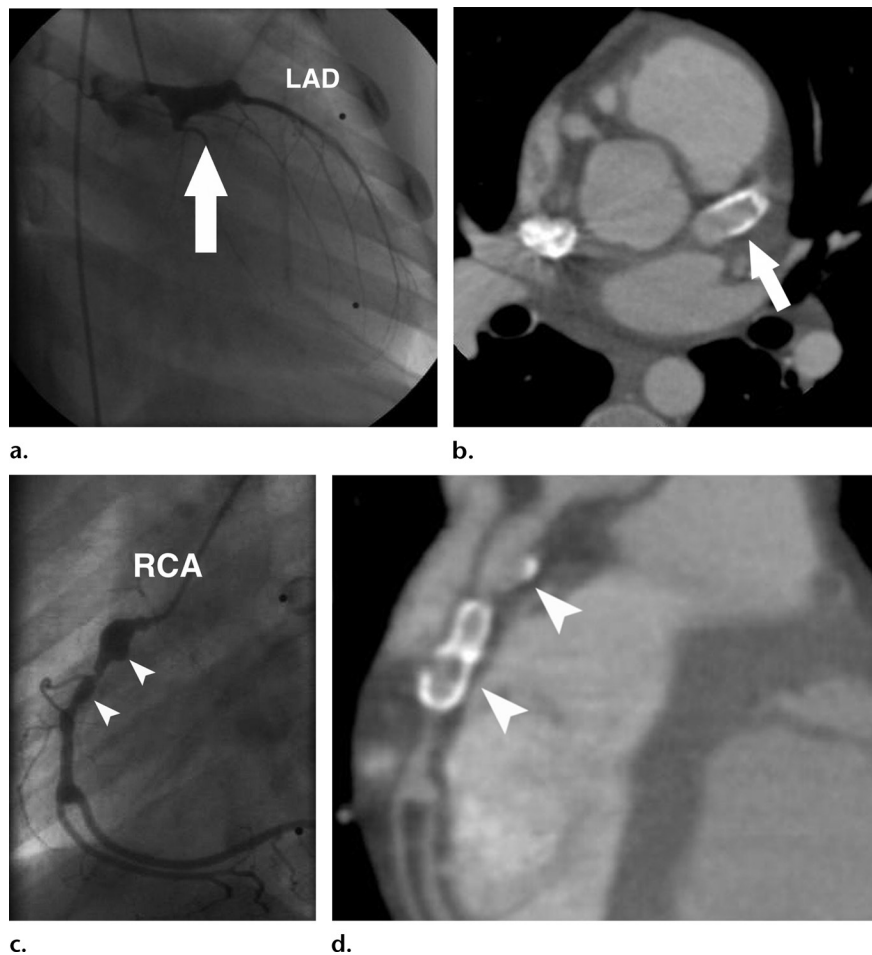


Figure 17. Kawasaki disease in a 10-year-old boy. (a, b) Right anterior oblique conventional angiographic image obtained with select injection of the left main coronary artery (a) and axial collimated CT angiographic image (b) show a peripherally calcified aneurysm (arrow) of the distal left main coronary artery and proximal LAD. (c, d) Left anterior oblique conventional angiographic image (c) and CT angiographic curved planar reconstruction image (d) of the RCA show several CAAs (arrowheads) that contain peripheral calcification and nonocclusive mural thrombus.

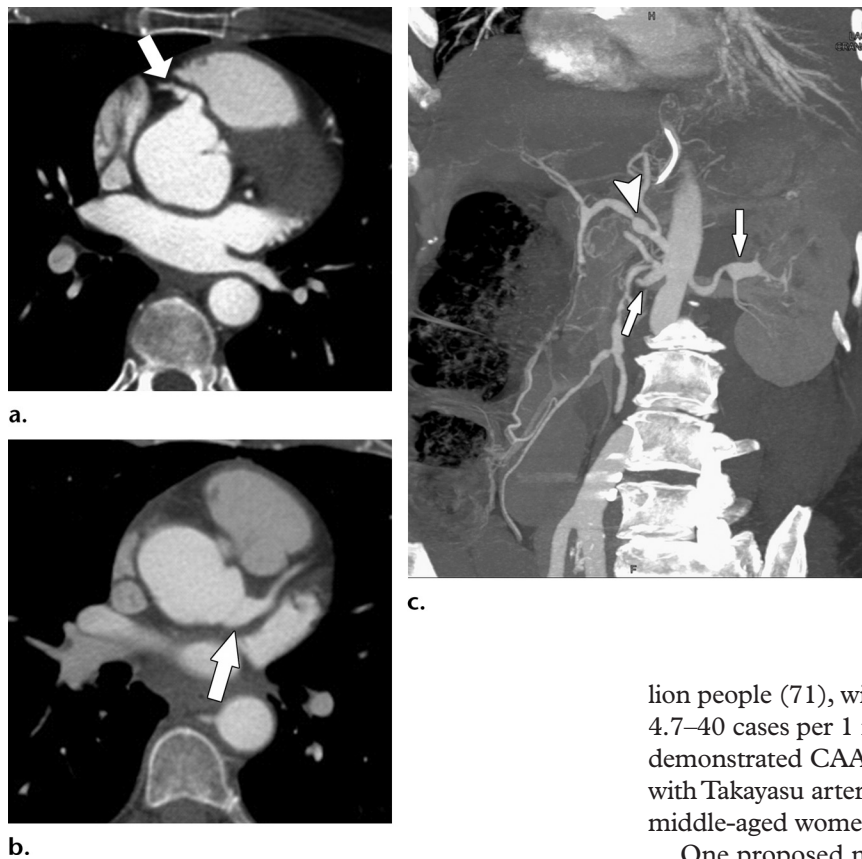


Figure 18. Takayasu arteritis in a 31-year-old patient with atypical chest pain. (a, b) Axial CT angiographic images (b obtained slightly superior to a) at the takeoff of the RCA (a) and at the takeoff of the left main coronary artery (b) show CAAs in the proximal RCA (arrow in a) and the left main coronary artery (arrow in b). (c) Coronal maximum intensity projection CT angiographic image of the abdomen and upper pelvis shows aneurysms of the renal arteries (arrows) and hepatic artery (arrowhead). The findings at histopathologic examination disclosed necrotizing aortitis and helped confirm the clinical diagnosis of Takayasu arteritis.

Superficial and deep vein thrombosis, caval and hepatic vein thrombosis, and pulmonary artery and thoracic aortic aneurysms are also seen in patients with Behçet disease and support the diagnosis (56,66,67).

Mortality in patients with Behçet disease is often due to rupture of vascular aneurysms (especially pulmonary artery aneurysms), intestinal ulcer perforation, Budd-Chiari syndrome (hepatic vein thrombosis), and myocardial dysfunction (56).

Takayasu Arteritis

Takayasu arteritis is a large-vessel vasculitis of unknown etiology that involves the aorta and branch vessels, although medium-sized pulmonary and coronary arteries may also be affected (68). Diagnosis is based on criteria set by the American College of Rheumatology (69). The disease often has two clinical phases: an acute systemic “prepulselessness” phase and a later “occlusive” phase. However, in almost half of the patients, the early phase is unrecognized, and instead there is a prolonged and fluctuating clinical course (70). Subacute and chronic complications include vascular stenosis, aneurysm, and occlusion. Although young women of Asian descent are the largest group affected, Takayasu arteritis has been described in both sexes and in many countries around the world (69). The annual global incidence is 1–2 cases per 1 mil-

lion people (71), with reported prevalence rates of 4.7–40 cases per 1 million (72,73). Kang et al (69) demonstrated CAAs in nine of 111 patients (8.1%) with Takayasu arteritis, most often in young or middle-aged women.

One proposed mechanism of CAA formation in Takayasu arteritis is the direct extension of the aortic inflammatory process into the coronary ostia and proximal coronary arterial segments (74). Thickening of the ascending thoracic aorta during the acute phase of disease increases the likelihood of coronary ostial stenosis (69), which is suggestive of a contiguous path of coronary arterial inflammation. The findings in several published cases and autopsy reports support this proximal predilection for coronary disease in patients with Takayasu arteritis; and, not surprisingly, this location is the most common site for CAAs in Takayasu arteritis (11,75). Premature atherosclerosis in the setting of chronic vasculitis may be a predisposing factor for CAAs, in addition to the primary inflammation (69).

Early diagnosis in this disease improves prognosis, and radiologic evaluation plays an important role. CT findings during the acute phase include concentric mural thickening and enhancement of the vessel walls, chiefly affecting the aorta and branch vessels but also occasionally the pulmonary and coronary arteries (68) (Fig 18). Conventional catheter angiography may be performed to assess coronary artery morphologic structure, but coronary CT angiography is an excellent noninvasive tool, particularly if cardiac symptoms are present. In the results of one large series ($n = 111$), almost 30% of patients with Takayasu arteritis experienced cardiac symptoms, and more than half (53%) of all patients

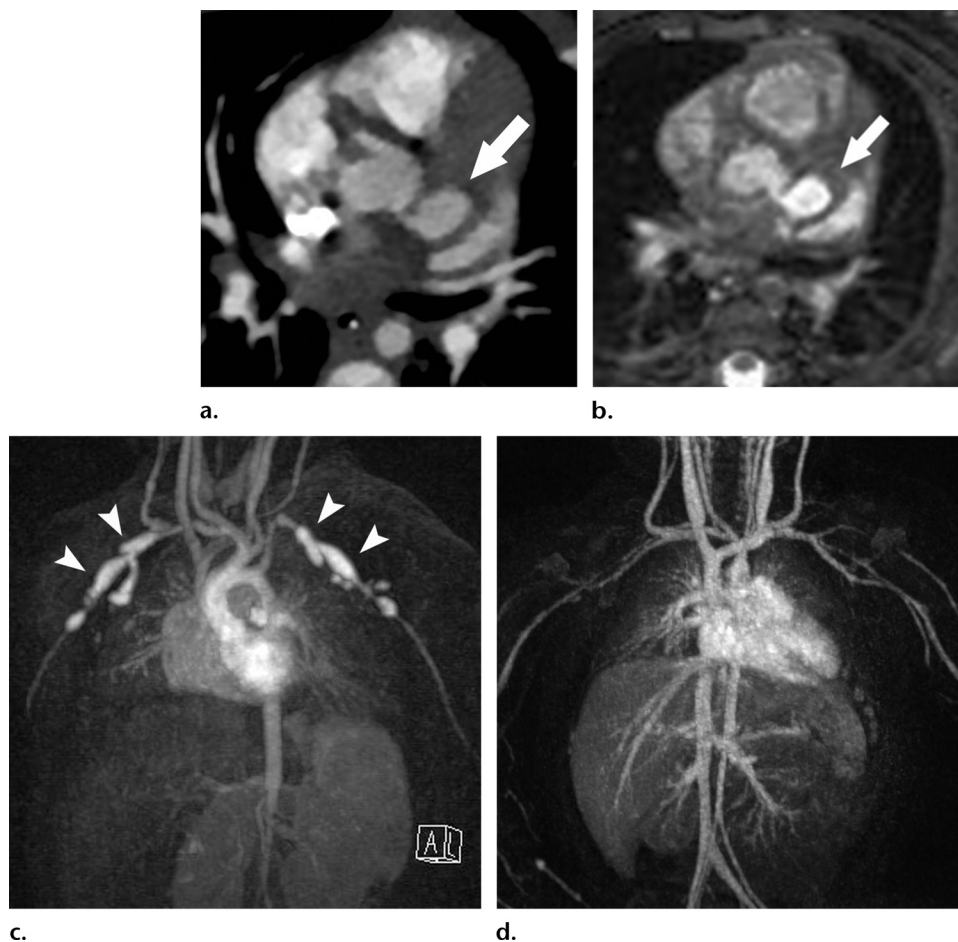


Figure 19. Takayasu arteritis. (a, b) Axial CT angiographic image (a) and axial steady-state free precession MR image (35/1.54; 60° flip angle; FOV, 256 × 256) (b) depict a saccular aneurysm (arrow) of the left main coronary artery. (c) Coronal three-dimensional MR angiographic image (2.63/0.97; 25° flip angle; FOV, 300 × 300) depicts an aneurysm of the left main coronary artery, as well as numerous aneurysms of both subclavian arteries (arrowheads). (d) Coronal MR angiographic image (2.63/0.97; 25° flip angle; FOV, 300 × 300) obtained 6 months later, after therapy, shows resolution of the previous multifocal aneurysms.

had coronary arterial abnormalities at coronary CT angiography, including ostial stenosis (28%), nonostial stenosis (37%), and aneurysm (8%). In this series, the presence and severity of coronary arterial lesions did not appear to correlate with disease acuity or severity, but notably, the coronary findings were more often found in older hypertensive patients with prolonged disease (mean duration, 17.8 years) (69).

In the later phase of Takayasu arteritis, CT may also demonstrate that the walls of large and medium vessels contain dystrophic calcification with skipped areas of fixed stenosis, often paired with enhancing collateral vessels. MR imaging may show increased signal intensity in thickened vessel walls and pericardial linings, intravascular thrombi, thickening of aortic valve leaflets, and aortic regurgitation. MR imaging and MR angiography are excellent modalities for surveillance in patients with Takayasu arteritis, to minimize ionizing radiation exposure (68) (Fig 19).

Giant cell arteritis (discussed in the following section) is almost always included in the differential diagnosis for Takayasu arteritis, although giant cell arteritis more often affects women at a more advanced age; Takayasu arteritis and giant cell arteritis appear to be closely related and may even be the same disease with different peaks in age incidence (76,77). In the results of one study, investigators found that patients with Takayasu arteritis are more likely to have carotid and mesenteric vessel involvement, and giant cell arteritis is more likely to affect axillary vessels (77). Findings of pulmonary artery involvement at CT or MR imaging may expand the differential diagnosis to include Behçet disease, depending on the clinical scenario (68).

Giant Cell Arteritis

Giant cell arteritis is a large-vessel vasculitis primarily affecting the aorta and its branch vessels, but giant cell arteritis also has a predilection for

medium vessels, including the carotid, axillary, vertebral, and ophthalmic arteries. Giant cell arteritis can also affect the temporal artery, but not in all patients (76,77). Giant cell arteritis is the most common primary systemic vasculitis in adults, usually affecting female patients older than 50 years (71). The annual incidence in North America is 20 cases per 100 000 patients older than 50 years, and giant cell arteritis chiefly occurs in the Causasian population (78). The overall prevalence of cardiac involvement in giant cell arteritis is low (<5%), with an unknown incidence of CAA formation (79). When present, coronary arterial involvement is presumably related to the adjacent aortic inflammatory disease in a pattern similar to that in other major branch vessels.

Clinical manifestations can range from a mild headache to critical end-organ ischemia, such as stroke, vision loss, and arm claudication; mortality from ruptured aortic aneurysms is similar to the mortality from ruptured aneurysms of other causes (71). Symptoms of myocardial ischemia in a patient with giant cell arteritis should prompt coronary artery imaging as well as testing for elevated levels of inflammatory markers. Steroids and immunosuppressive agents are administered to treat giant cell arteritis. Despite complications from the disease and long-term treatment, investigators in one study found no difference in mortality between patients with giant cell arteritis and a control group (78).

Polyarteritis Nodosa

Polyarteritis nodosa is a systemic necrotizing vasculitis of medium arteries, typically without small-vessel inflammation such as glomerulonephritis. Polyarteritis nodosa is not associated with antineutrophil cytoplasmic antibodies (ANCA), which helps to distinguish this disease from the ANCA-associated vasculitides (76). In most cases, the etiology is unknown, but viruses such as the hepatitis B virus have been implicated (80). The annual incidence of polyarteritis nodosa ranges from 1.6 to 3.6 cases per 1 million people (81,82), with a prevalence of 31 cases per 1 million (83), which is lower than the rates of other systemic vasculitides. Polyarteritis nodosa has no gender predisposition and usually manifests in the 5th or 6th decade of life. Renal disease is common and potentially severe (82). Polyarteritis nodosa-related cardiac involvement is unusual and ranges from no symptoms to symptoms related to congestive heart failure, acute coronary syndrome, myocardial infarction, or sudden cardiac death (80,84).

Well-recognized vascular complications of polyarteritis nodosa include small fusiform or saccular aneurysms ranging in size from 1 to 5 mm, which

are typically centered in the renal, mesenteric, and hepatic arteries (80). CAAs are rare; and in the results of limited case reports, investigators describe solitary or multiple lesions, with one or more coronary arteries involved, and a variable amount of endoluminal thrombus (84–88).

Rheumatoid Arthritis

Rheumatoid arthritis is the most common inflammatory arthritis and affects peripheral synovial joints. Of all of the inflammatory arthritides, rheumatoid arthritis manifests the most widely recognized component of vasculitis (89). Systemic rheumatoid vasculitis affects vessels of all sizes, most often occurs in patients older than 60 years of age with chronic rheumatoid factor–positive erosive arthritis, and affects males more than females (89). In the results of multiple studies, investigators have demonstrated an overall decline in rheumatoid vasculitis since the 1990s, which is likely related to earlier more-aggressive treatment of the disease (90). Although symptomatic coronary arteritis is rare, discerning the predisposing conditions for cardiac disease in patients with rheumatoid arthritis has proved challenging, and the investigation continues (91).

The literature about CAAs in patients with rheumatoid arthritis is quite limited. In the results of one report, ectasia of the left circumflex coronary artery evolved into a 2.3-cm CAA in one patient 6 months after a lapse in immunosuppressive therapy. In the setting of elevated levels of inflammatory markers, this aneurysm was complicated by a partly occlusive thrombus, leading to a myocardial infarction without ST-segment elevation (92). In another report, investigators described administration of systemic thrombolytic therapy for an acutely thrombosed 1.5-cm CAA of the RCA in a patient with rheumatoid arthritis who had myocardial ischemia (93). Presumably, rheumatoid arthritis–related CAAs develop as a consequence of vasculitis, although underlying accelerated atherosclerosis may be complicit (91). In patients with long-standing rheumatoid arthritis and symptoms of acute myocardial ischemia, a thrombosed or partially thrombosed aneurysm should be excluded, particularly if an active inflammatory state exists.

Genetically Associated Vasculopathies

CAAs may develop in the context of genetically inherited disorders, without underlying advanced atherosclerosis. Vasculopathies associated with a spectrum of heritable disorders appear to affect the cardiovascular system and, specifically, the coronary arteries. These disorders are characterized by mutations in transforming growth factor (TGF)– β receptors and abnormalities in the extracellular matrix, which disrupt the integrity

of vessel walls. TGF- β signaling is an established modulator of extracellular matrix structure and composition. Such mutations are believed to result in aneurysmal dilatation and dissection, most notably of the ascending aorta but also within the coronary arteries (94–96).

Among the genetically inherited causes of CAAs are Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, neurofibromatosis type 1, autosomal dominant polycystic kidney disease (ADPKD), hereditary hemorrhagic telangiectasia, and bicuspid aortic valve. Although these disorders have overlapping features, careful clinical assessment usually enables a diagnosis that can be validated with genetic testing.

Marfan Syndrome

Marfan syndrome is an autosomal dominant disorder of the connective tissue, with high penetrance and variable severity. The incidence of Marfan syndrome is around 2–3 cases per 10 000 individuals (97). Marfan syndrome is associated with mutations in the gene for fibrillin 1 (*FBN1*), homologous to the family of latent TGF- β binding proteins (98). The *FBN1* mutations result in dysregulation of TGF- β , leading to disordered elastic fiber formation in the aortic wall, a characteristic of cystic medial degeneration (99). Cystic medial degeneration is a common feature of aneurysms in Marfan syndrome, and so its presence in a CAA may indicate a congenital genetic defect that causes an excess of active TGF- β . Nearly all adult patients with Marfan syndrome have abnormalities in the cardiovascular system, which account for more than 90% of premature deaths in patients with Marfan syndrome (100).

The major cardiovascular manifestation in Marfan syndrome is a progressive dilatation of the ascending aorta, leading to aortic aneurysm formation and, eventually, to fatal aortic rupture or dissection if there is no intervention. CAAs are rare but have been described in case reports (31,101–104). Becker and van Mantgem (103) performed an autopsy study of patients with Marfan syndrome and found histologic changes in the wall of the coronary arteries similar to changes noted in the aortic wall. Interestingly, the development of coronary ostial aneurysm is a documented complication noted after elective aortic root replacement, suggesting contiguity of aortic microstructural abnormalities within the ostial and proximal segments of the coronary arteries (102,103,105,106) (Fig 20). Meijboom et al (106) reported that such postoperative coronary ostial aneurysms were more frequent in patients who were 35 years of age or younger (56%) at the time of surgery, compared with those older than 35 years of age (15%).

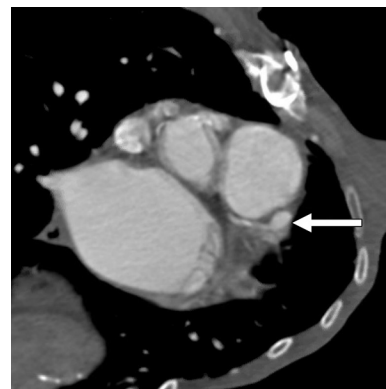


Figure 20. Marfan syndrome. Oblique axial CT angiographic image shows repair of an ascending aortic aneurysm associated with a CAA (arrow) in the mid LAD. (Image courtesy of Andrew J. Bierhals, MD, MPH, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, Mo.)

Loeys-Dietz Syndrome

Loeys-Dietz syndrome is a rare autosomal dominant inherited genetic disorder characterized by premature and aggressive systemic aneurysms and dissections. Vascular complications are noted frequently and can result in early death (107–109). In one cohort ($n = 40$), 98% of patients had aortic root aneurysm, 84% had arterial tortuosity, and 52% had nonaortic aneurysms. Median survival for this cohort was 37 years, with a mean age at death of 26 years (107). Vessel wall analysis of patients with Loeys-Dietz syndrome demonstrates loss of vascular smooth muscle cells and a marked excess of collagen. These histopathologic findings are suggestive of a severe defect in elastogenesis, rather than secondary elastic fiber destruction.

Loeys-Dietz syndrome is associated with mutations of the genes encoding the TGF- β receptor 1 or 2 (*TGFBR1* or *TGFBR2*), which lead to upregulation of TGF- β expression and degradation of the arterial medial layer. Two phenotypes of the disorder exist, and both forms express generalized arterial tortuosity and the predisposition to arterial dissection, aneurysm, and rupture. Patients with Loeys-Dietz syndrome type I have craniofacial abnormalities (craniosynostosis, cleft palate, or hypertelorism), along with aortic root aneurysms, aneurysms of other vessels, arterial tortuosity, arachnodactyly, pectus deformity, scoliosis, joint laxity, and developmental delay. Patients with Loeys-Dietz syndrome type II lack the craniofacial deformities but express cutaneous findings (velvety and translucent skin, easy bruising, and atrophic scars), as well as the arterial abnormalities noted in Loeys-Dietz syndrome type I (108,109).

Arterial aneurysms in patients with Loeys-Dietz syndrome have been observed in almost all branches of the aorta, including (but not limited to) the subclavian, renal, superior mesenteric, and hepatic arteries. Coronary artery involvement has also been described, but rarely, and includes aneurysm and dissection (110,111). The cause of death in patients with Loeys-Dietz syndrome is almost always cardiovascular complications, which include aortic dissection or rupture (thoracic or abdominal), intracerebral hemorrhage, and vascular ruptures in the spleen, uterus, or bowel. Patients with Loeys-Dietz syndrome type I have a slightly greater risk of death at an early age from cardiovascular complications, compared with patients with Loeys-Dietz syndrome type II (23 years vs 32 years, respectively) (107).

Vascular Ehlers-Danlos Syndrome (Ehlers-Danlos Type IV)

Ehlers-Danlos syndrome is a group of hereditary disorders caused by mutational defects in the gene encoding for type III procollagen. The pattern of inheritance may be autosomal dominant, autosomal recessive, or X-linked inheritance. The overall prevalence of Ehlers-Danlos syndrome is 1 case per 10 000 individuals, depending on the subtype (112). Several subtypes of Ehlers-Danlos syndrome have been described, almost all of which are associated with skin hyperflexibility and joint hypermobility (113,114).

Vascular Ehlers-Danlos syndrome (previously known as Ehlers-Danlos type IV) is an autosomal dominant variant that accounts for less than 4% of all cases of Ehlers-Danlos syndrome and usually has a poor prognosis. The disorder can affect medium and large arteries in any location and should be suspected in young patients presenting with unusual or extensive vascular findings. Unfortunately, in approximately 70% of patients, vascular rupture or dissection is a presenting sign (114).

By using CT, MR imaging, conventional angiography, and ultrasonography, Zillocchi and colleagues (115) found arterial aneurysms and dissections to be the most common imaging findings, followed by arterial ectasias and occlusions. Rare involvement of the coronary vessels may lead to either CAA or dissection (116). CAAs or vaso-occlusive disease as a result of coronary dissection should raise the possibility of Ehlers-Danlos syndrome in a patient with clinical features consistent with the diagnosis, and the results of genetic evaluation are confirmatory (29,116–118).

Neurofibromatosis Type 1

Neurofibromatosis type 1 is a common autosomal dominant disorder with a prevalence of

1:4000. The cardinal features of neurofibromatosis type 1 include multiple café au lait macules, benign neurofibromas, and iris hamartomas. Cardiovascular malformations may develop in patients with neurofibromatosis type 1, with a reported frequency ranging from 0.4% to 6.4% (119–121). Approximately 10 cases of neurofibromatosis with CAAs have been reported (122). The pathologic condition is presumably noninflammatory, because the results of studies of renal aneurysms associated with neurofibromatosis have shown a dysplastic-like artery with nodules of smooth muscle in the intima, without inflammation (122). Neurofibromatosis type 1 vasculopathy may affect vessels ranging in size from the proximal aorta to small arterioles and can lead to vascular aneurysms, pseudoaneurysms, rupture, occlusion, or stenosis (120,121,123).

The protein product of the neurofibromatosis type 1 gene, neurofibromin, is expressed in blood vessel endothelial and smooth muscle cells, and thus neurofibromatosis type 1 vasculopathy may be the consequence of altered neurofibromin function in cells that make up the vessel wall (120,123). Aneurysms or stenosis of the aorta and its main branches may occur in neurofibromatosis type 1, presumably owing to this vasculopathy. Among visceral arteries, the proximal renal arteries are most commonly affected, but sites of vasculopathy in the spleen, pancreas, meninges, small intestine, thyroid, and heart also have been noted (124).

CAAs in the setting of neurofibromatosis type 1 are a rare occurrence (Fig 21). Tins et al (125) characterized a 6-cm CAA in an asymptomatic patient with neurofibromatosis type 1 by using CT and MR imaging. Various case reports document a single CAA in living patients with neurofibromatosis type 1 (126–128), multiple CAAs (129–131), and coronary ectasia (132). Unfortunately, sudden death is a more common manifestation of neurofibromatosis type 1 with coronary artery involvement, usually owing to coronary thrombus formation and myocardial infarction (124,127,129,133–136).

Autosomal Dominant Polycystic Kidney Disease

Polycystic kidney disease is the most common inherited renal disorder caused by mutations in either *PKD1* or *PKD2*. *PKD1* encodes polycystin-1, and *PKD2* encodes polycystin-2. The *PKD1* mutation is responsible for 85% of cases of polycystic kidney disease, and the *PKD2* mutation for the remainder. Polycystic kidney disease may be inherited as either an autosomal dominant trait (as ADPKD) or an autosomal recessive trait, with the autosomal dominant trait more commonly

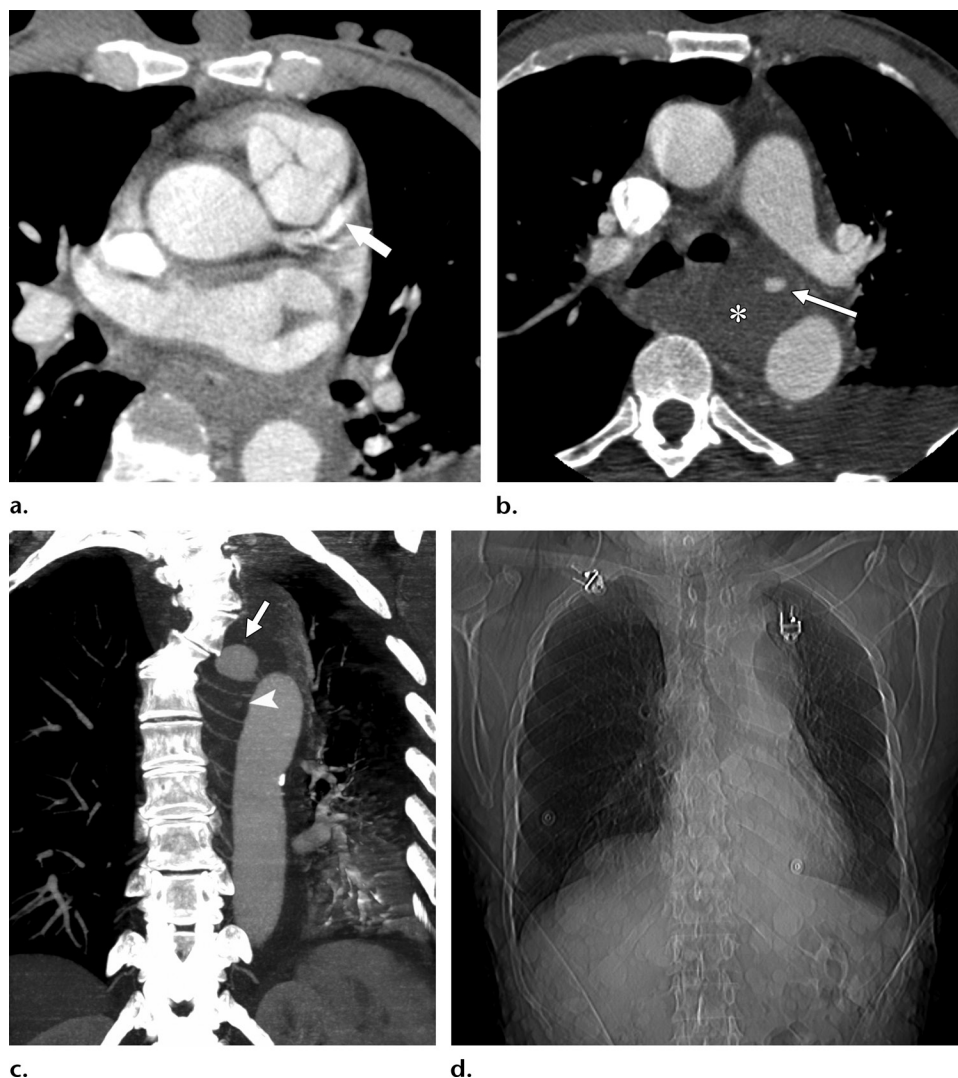


Figure 21. CAA in a 65-year-old patient with a history of neurofibromatosis type 1 who presented with mediastinal hemorrhage without a definitive source, considerable chest pain, and hypotension. (a, b) Axial CT angiographic images (b obtained superior to a) show ectasia of the LAD (arrow on a) and mediastinal hemorrhage (*) on b). A small aneurysm of an aortic collateral branch is depicted within the region of hemorrhage as a focus of contrast material (arrow on b). (c) Coronal MPR CT angiographic image shows a large intercostal aneurysm (arrow) and a subtle smaller intercostal aneurysm (arrowhead). (d) Scout CT image shows numerous neurofibromas involving the subcutaneous tissues.

expressed at an estimated prevalence of 1:1000 (137–139). Although ADPKD is characterized by kidney cysts and renal failure, it should be regarded as a systemic disease. The genetic defects of ADPKD appear to affect vascular wall integrity through alterations in the extracellular matrix, myofibroblasts, collagen, and polycystin (140). This may explain why ADPKD is associated with several cardiovascular abnormalities, including dilatation of the aortic root, dissection of the thoracic aorta, CAAs, atrial septal aneurysms, and mitral valve prolapse (138,141).

The prevalence of CAAs in patients with ADPKD is low but still higher than in the general population (141,142). About half of the reported cases of CAAs in ADPKD are saccular aneurysms, and the remainder are fusiform an-

eurysms (141). In the results of a 10-year retrospective review of coronary angiograms obtained in patients with end-stage renal failure, Chiha et al (140) found that 29 patients had ADPKD, and 15 patients had end-stage renal failure from other causes. The patients with end-stage renal failure who had ADPKD had coronary artery sizes larger than normal; the patients with end-stage renal failure who did not have ADPKD had luminal diameters closer to the normal ranges. According to Chiha et al (140), these findings suggest an underlying ADPKD-related vasculopathy. Investigators further propose that the larger-diameter coronary arteries predispose patients with ADPKD to myocardial ischemia and infarction owing to hemodynamic alterations within the coronary arteries (140,143).

Hereditary Hemorrhagic Telangiectasia

Hereditary hemorrhagic telangiectasia, or Rendu-Osler-Weber syndrome, is an autosomal dominant disorder affecting approximately one in 5000 people. Hereditary hemorrhagic telangiectasia is characterized by telangiectasias and arteriovenous malformations. Similar to other pathologic conditions that may result in a CAA, hereditary hemorrhagic telangiectasia is most commonly caused by mutations within TGF- β receptors that disrupt normal TGF- β signaling, thus inducing characteristic vascular and connective tissue defects. Manifestations of hereditary hemorrhagic telangiectasia typically are not present at birth and develop with time. Telangiectasias in the nasal mucosa are the most common manifestation and usually the earliest symptom of hereditary hemorrhagic telangiectasia (144,145). These telangiectasias increase in number and size with age (146).

Involvement of the coronary arteries in association with hereditary hemorrhagic telangiectasia has been described in isolated case reports (147–150). In these cases, coronary ectasia and CAAs have been detected, but atherosclerotic disease is absent. Small coronary arteriovenous malformations have also been reported and are similar in appearance to angiodysplastic lesions noted elsewhere in the body (149). The characteristic vascular and connective tissue defects may rarely lead to coronary dissection in patients with hereditary hemorrhagic telangiectasia (151).

Bicuspid Aortic Valve

Bicuspid aortic valve is a heritable disorder with a reported increased risk of CAAs. The pattern of inheritance is autosomal dominant with incomplete penetrance, occurring in 0.46%–1.37% of the population (152). Up to 50%–70% of patients with bicuspid aortic valve develop dilatation of the aortic root and ascending aorta (152,153). Similar to Marfan syndrome, the coronary arteries of patients with bicuspid aortic valve share common histopathologic characteristics, including degeneration of the medial layer, decreased fibrillin-1 in the vessel wall, loss of smooth muscle cells, and increased matrix metalloproteinase activity (152,154). An important additional consideration is that the aortic valve, proximal segments of the coronary arteries, the ascending aorta, and the pulmonary trunk share a common embryonic origin from neural crest cells (152,155).

Meindl et al (156) evaluated 94 patients with bicuspid aortic valve and found an increased incidence of CAA and ectasia in patients with bicuspid aortic valve, both with and without evidence of ascending aortic ectasia. In additional

case reports, investigators have uncovered similar observations and have highlighted the importance of further investigation of the association between coronary and ascending thoracic aortic disease in patients with bicuspid aortic valve (157).

Mycotic, Iatrogenic, and Drug-related Aneurysms

Mycotic Aneurysms

A mycotic coronary aneurysm is a septic dilatation of the coronary arterial wall. *Mycotic aneurysm* was traditionally a term used for infected aneurysms arising from bacterial endocarditis or an infected aneurysm of the sinus of Valsalva (158,159). It is now well recognized that mycotic CAAs are frequently associated with sepsis, bacteremia, or endocarditis (160,161). Bacterial agents are reported to be the most common cause of mycotic CAAs, but mycotic CAAs are also found in patients with human immunodeficiency syndrome, syphilis, viral infection (Epstein-Barr virus), or fungal infection (162–164). More recently, mycotic CAAs have occurred after percutaneous coronary interventions (164,165).

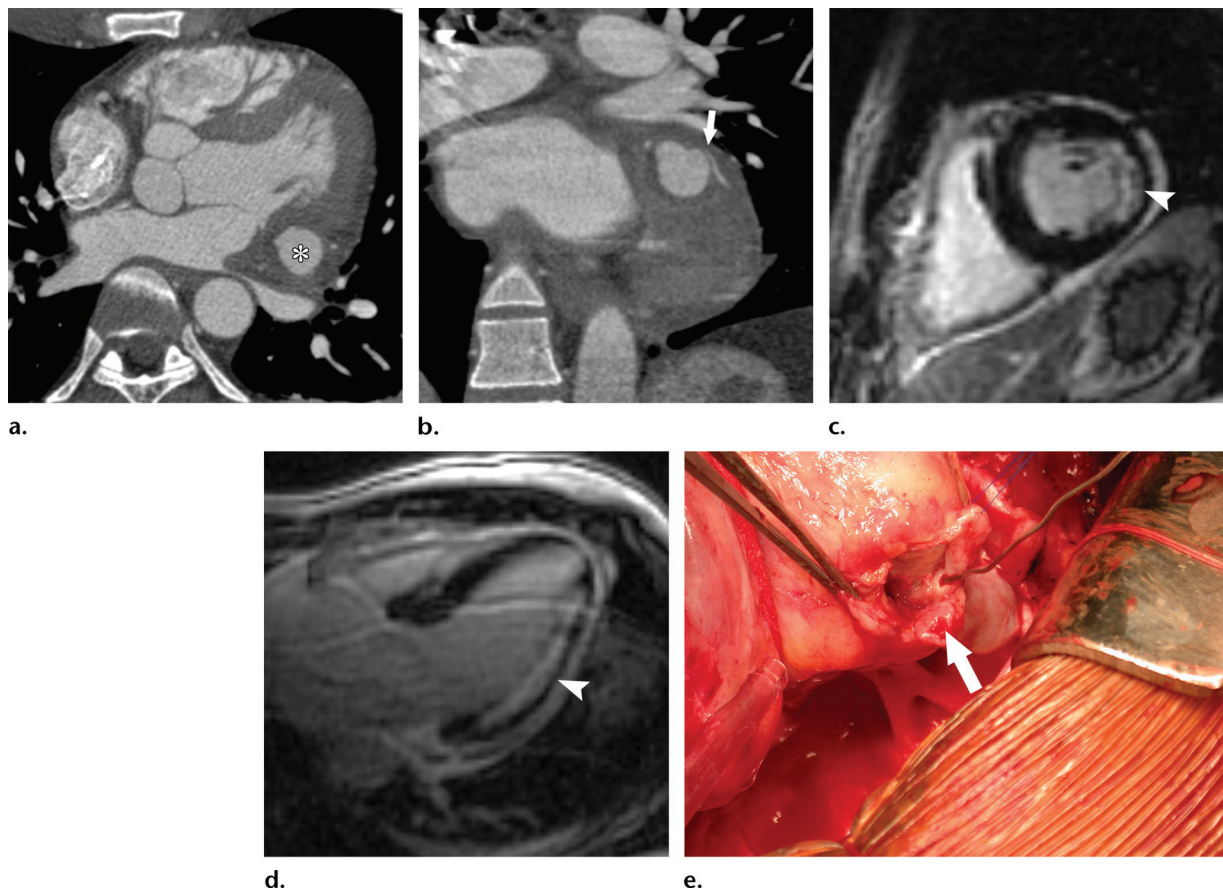
Mycotic CAAs can be difficult to diagnose owing to their low incidence and variable manifestations. In the results of multiple case reports and small studies, investigators indicate that patients can present with fever of unknown origin, leukocytosis, positive blood cultures, an elevated erythrocyte sedimentation rate or C-reactive protein level, or endocarditis (160). In rare cases, patients present with the complications of cardiac ischemia and/or cardiac tamponade (166) (Fig 22).

Optimal imaging modalities include coronary CT angiography and cardiac MR imaging and/or MR angiography. Unlike interventional coronary angiography, coronary CT angiography demonstrates thrombosed, stenotic, and patent vessel segments. CT angiography may also reveal related complications, including coronary thrombosis, pulmonary embolism, fistula formation, arterial rupture, and hemopericardium. Cardiac MR imaging, with the use of a combination of cine imaging and free-breathing navigator whole-heart three-dimensional MR angiography, has also been reported as a valuable imaging tool because of the excellent tissue characterization depicting the aneurysmal wall changes (166). Nevertheless, mycotic and nonmycotic aneurysms are difficult to distinguish on the basis of imaging alone. To make this distinction, imaging findings should be combined with the clinical history and markers of infection to favor a mycotic cause.

Figure 22. Mycotic CAA associated with hypereosinophilia in a 39-year-old woman who presented with chest pain. (a) Axial coronary CT angiographic image shows multiple large CAAs (arrows), some as large as 14 mm in diameter, involving the ostial part of the LAD. (b) Curved MPR CT angiographic image shows associated luminal layered thrombus (arrow) in the proximal LAD, instead of inflammatory tissue. (c) Three-dimensional volume-rendered CT angiographic image better shows the distribution of ectatic and aneurysmal involvement (arrowheads) of the LAD. (Image courtesy of Marcus Chen, MD, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Md.)



Figure 23. CAA in association with drug abuse in a 26-year-old man with a history of cocaine abuse who presented with chest pain and a diagnosed non-ST elevation myocardial infarct. (a) Axial CT angiographic image shows a round enhancing structure (*) in the region of the left circumflex coronary artery. (b) Oblique coronal maximum intensity projection CT angiographic image shows an obtuse marginal branch in direct communication with the structure (arrow). (c, d) Short-axis (c) and three-chamber (d) inversion-recovery MR images (435/3.23; 25° flip angle; FOV, 399 × 399) show delayed subendocardial enhancement (arrowhead) in a left circumflex coronary artery distribution. (e) Photograph obtained during surgery shows the aneurysm, with exposure of the ostium (arrow). The patient underwent closure of the CAA and a coronary artery bypass grafting procedure.



Iatrogenic Aneurysms

An iatrogenic aneurysm arises secondary to an intravascular intervention that injures the vessel wall with a focal tear, occasionally complicated by dissection (167). Incomplete healing of the defect may progress to aneurysm formation, sometimes within just a few days after the initial injury (168). Percutaneous transluminal coronary angioplasty with high-pressure balloon inflation, directional coronary atherectomy, and laser angioplasty are all associated with the development of CAAs. The incidence is rare, ranging from 0.3% to 6.0% (168).

The placement of drug-eluting stents and older-generation bare metal stents has also been implicated in the formation of postprocedural CAAs (168,169). In large randomized trials, 0.8%–1.1% of patients with a drug-eluting stent or bare metal stent develop a CAA (168). The drug-eluting stents release agents to prevent stent thrombosis, but a side effect appears to be inhibition of vascular wall healing (ie, re-endothelialization). Further, the chemical polymers released by drug-eluting stents may induce inflammation and even hypersensitivity within the wall of the injured vessel (168). Stents may also be a source of infection, leading to coronary wall inflammation and damage (170).

CAAs associated with stent placement manifest at varying times, and thus patients can be grouped into three categories (168). A type I CAA forms within the first 4 weeks and may lead to pericarditis. A type II CAA is more subacute or chronic and is typically detected more than 6 months after stent placement. Patients in this category may be asymptomatic or may experience angina (168). A type III CAA is superinfected (mycotic); and typically, systemic signs exist to suggest the diagnosis, including fever (168).

Iatrogenic CAAs are typically saccular and adjacent to the intervention site. If the CAA is associated with stent placement, it arises along the course of the stent. There may be thrombosis of the stent or a slow flow of contrast material along the course of the stent (168).

Cocaine Abuse

Cocaine, derived from the coca plant, is an illicit recreational substance that may be snorted, injected, or inhaled. Its use is associated with important cardiovascular complications. Powerful cocaine-induced adrenergic stimulation leads to tachycardia, hypertension, and coronary artery vasoconstriction. Myocardial ischemia, infarction, and sudden cardiac death may follow. In some cases, the episodic coronary vasospasm is accompanied by in situ coronary thrombosis

and embolic phenomena (171). In the results of autopsy studies, investigators have found that cocaine abusers have accelerated atherosclerosis for reasons that are not clear, although endothelial dysfunction is implicated (171,172) (Fig 23).

In the results of one large study of patients with a history of cocaine abuse and prior coronary angiography ($n = 112$), the prevalence of CAA was remarkably high (30%), particularly in view of the overall younger age of cocaine abusers (mean age, 44 years) (172). Most patients in this study were male (80%), had hypertension (73%), and were smokers (95%). Previous myocardial infarctions were documented in 45% of the cocaine abusers, even though almost half of abusers had angiographically normal coronary arteries. Satran et al (172) postulated that some considerable numbers of the prior myocardial events in these patients were the consequence of intense vasoconstriction, possibly complicated by occlusive thrombosis. Satran et al (172) further proposed that the higher risk of CAA formation in cocaine abusers may be related to repeated episodes of severe hypertension and intense coronary vasoconstriction, which causes endothelial damage. The role of accelerated atherosclerosis in these patients is less certain, and further investigation is recommended (172).

Imaging Assessment of CAAs

Imaging is optimized for depiction of coronary artery anatomy, and imaging modalities include electrocardiographically gated CT angiography, MR imaging and/or MR angiography, trans-thoracic echocardiography, and angiographic cardiac catheterization. Assessment of a CAA includes evaluation of its shape and structure, including morphology (fusiform or saccular), aneurysm diameter, wall calcification, luminal thrombosis, and any significant stenosis. The origin and termination of the CAA are determined. The description should further note whether the CAA is singular or multiple, as well as the name of the precise segmental coronary artery (or arteries) involved. Finally, the search should exclude potential complications, including myocardial perfusion abnormalities, fistula formation, appreciable extrinsic mass compression, or evidence of active rupture, including hemopericardium (173).

In many cases, the radiologic findings of a CAA do not point to a specific underlying disease. However, some conditions have typical features that may be suggestive of a specific cause (Table). For example, an ACAA is suggested by the presence of calcified atherosclerotic plaque in other vessels, including the aorta. Kawasaki disease is characterized by multiple CAAs

Characteristic Features of CAAs

Cause of CAA*	Single or Multiple CAAs	Saccular or Fusiform	Mural Calcification	Luminal Thrombosis	Additional Helpful Findings
Atherosclerosis	Up to two-thirds are multiple	Fusiform	Present	Present	Evidence of coronary stenosis and plaque, atherosclerotic plaque in other vessels, myocardial ischemia or infarct
Congenital	Single	Saccular	Variable	Variable	Often discovered incidentally
Kawasaki disease	Multiple	Not documented	Present (when chronic)	Present	History of febrile illness, mucocutaneous lymph node syndrome (usually <5 yr old)
Takayasu arteritis	Variable	Not documented	Present (when chronic)	Not documented	Aneurysms located at coronary ostia, aortic wall thickening and enhancement
Behçet disease	Variable	Not documented	Absent	Present	Systemic findings, including deep venous thrombosis, pulmonary artery aneurysms, oral ulcers, and uveitis
Mycotic or septic	Variable	Variable	Present (when chronic)	Variable	Supportive evidence of systemic infection, bacteremia, immunocompromise
Iatrogenic	Single	Saccular, with or without dissection	Absent	Variable	Occurs at site of intervention or other vascular injury, may develop hours to months later

*Other inflammatory and noninflammatory causes: Dedicated histopathologic and radiologic studies are limited. In these suspected cases, inflammation biomarkers and/or genetic evaluations are usually confirmatory.

marginated with rims of calcification in a child or young adult. A mycotic CAA may be found in the setting of an immunocompromised patient and/or a patient with bacteremia. Patients with a history of cocaine abuse are at considerable risk for the development of CAAs. In more unusual cases, a CAA is the consequence of a primary inflammatory vasculitis or a noninflammatory inherited vasculopathy and/or connective tissue disease. The differential diagnosis of a CAA includes a sinus of Valsalva aneurysm, an aneurysm of a surgically placed coronary arterial or venous graft, and a neoplastic process centered in the heart, pericardium, or mediastinum.

Conclusion

Most often, CAAs are discovered incidentally. Symptomatic patients present with complications related to coronary artery inflammation and thrombosis, including myocardial ischemia and infarction, embolism, rupture, or fistulization. The most common cause of CAAs in adults is atherosclerosis and in children is Kawasaki disease. Although helpful imaging features exist that are suggestive of these conditions, in general, distinguishing among the different causes of CAAs may be difficult on the basis of the imaging appearance alone. Clinical factors (including patient age, sepsis, underlying systemic

disease, coexisting coronary artery disease, and a prior febrile illness in early childhood) often more reliably point to the underlying cause.

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