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Myocardial infarction in a 24-year-old woman

A HEALTHY 24-YEAR-OLD woman suddenly developed severe fatigue and substernal discomfort, beginning 8 hours earlier. An electrocardiogram showed serial changes consistent with an inferior wall infarction. Her creatine kinase (CK) level was 246 IU/mL (normal range 30–120) with a cardiac fraction of 33 IU/mL (normal range 0–8 IU/mL). She had smoked 1/2 pack of cigarettes per day for the past 5 years. She was not using oral contraceptives. She had no family history of heart disease. Her blood lipid profile was unknown.

WHAT IS THE CAUSE OF THIS PATIENT'S MI?

1 Causes of myocardial infarction (MI) in young patients include which of the following?

- ☐ Atherosclerosis
- ☐ Cocaine abuse
- ☐ Congenital coronary anomalies
- ☐ Infective endocarditis
- ☐ All of the above

Approximately 2% to 6% of MIs occur in patients under age 45; women account for about 20% of patients under age 55 with MI.¹ Causes of MI in young patients include all of the above.

Atherosclerosis. Most young patients with MI have coronary atherosclerosis.² MI in the absence of atherosclerosis, although uncommon in older patients, accounts for approximately 20% of cases in patients under age 45 (TABLE 1).

Cigarette smoking is much more common in young MI patients: 76% to 91% of young MI patients smoke, compared with approximately 40% of older patients with MI.

The most prevalent pattern of lipid abnormalities in young MI patients appears to be homozygous familial hypercholesterolemia, in which low-density lipoprotein (LDL) is elevated but levels of high-density lipoprotein (HDL) and triglycerides are normal. Familial combined hyperlipidemia (in which LDL and triglycerides are both elevated) is also seen.³ Hypertension and diabetes mellitus are less frequent in younger MI patients than in older MI patients.^{4,5}

TABLE 1

Risk factors and causes of MI in young patients (≤ 45 years)

RISK FACTORS AND CAUSES	PREVALENCE
Atherosclerosis	80%
Coronary artery embolism	5%
Patent foramen ovale	
Bacterial endocarditis	
Hypercoagulable states	5%
Oral contraceptives	
Systemic lupus erythematosus	
Inherited defects	
Congenital coronary artery anomalies	4%
Other	6%
Coronary artery dissection	
Coronary artery spasm (including cocaine abuse)	
Blunt chest trauma	
Vasculitis	
Systemic hemorrhage, hypotension	

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Cocaine abuse is a well-recognized and prominent risk factor for MI in young patients, especially with “crack” cocaine, the highly addictive freebase form of the drug.⁶ Possible mechanisms include acute drug-induced increases in heart rate and blood pressure and decreased coronary blood flow from vasospasm. The resultant mismatch between myocardial oxygen supply and demand, coupled with increased platelet hyperaggregability induced by the drug, causes myocardial ischemia and infarction.⁷ Chronic cocaine use can also accelerate atherosclerosis, and it can cause direct myocardial toxicity that manifests as focal myocardial necrosis. Young patients presenting with symptoms suggestive of myocardial ischemia or panic attacks should be questioned about and tested for cocaine use.

Congenital coronary anomalies account for approximately 4% of MIs and sudden deaths in young patients.⁸ These abnormalities include arteries that tunnel deep through the myocardium instead of resting on top of it (a condition that presumably reduces blood flow during systole), an origin from the wrong coronary sinus, aneurysms, and coronary artery ostial obstructions.

Infective endocarditis causing coronary embolism is a well-recognized cause of MI.⁹

Other causes of MI in young patients include spontaneous coronary artery dissection, which is seen predominantly in women¹⁰; coronary arteritis in vasculitic systemic disorders such as systemic lupus erythematosus (SLE)¹¹; and blunt chest trauma causing coronary thrombosis or dissection.¹²

In SLE, premature atherosclerosis is thought to be caused by immune-mediated endothelial injury, hyperlipidemia, and hypertension. The hypertension may be related to steroid therapy. In addition, hypercoagulability resulting from the lupus anticoagulant is another potential mechanism for coronary thrombosis.

MI has also been described in association with prior mediastinal radiation therapy for Hodgkin disease and other neoplasms.

History and cardiac evaluation

The patient denied any cocaine use. She had

no history of hypertension or diabetes, and no family history of hyperlipidemia. There was no history of fever, night sweats, or weight loss to suggest infective endocarditis.

An echocardiogram showed a well-encapsulated, homogeneous mass measuring 6 cm by 5 cm in the region of the tricuspid annulus. The mass, which extended from the annulus along the right atrial free wall and just below the right atrial appendage, appeared to be within the pericardial sac adjacent to the right atrial free wall. The inferior wall was regionally hypokinetic, with a mildly depressed estimated ejection fraction of 50%.

CAUSES OF CARDIAC MASSES

2 All of the following can cause MI and a cardiac mass, except which one?

- ☐ Cardiac tumors
- ☐ Coronary aneurysms
- ☐ Cardiac cyst
- ☐ Infective endocarditis

Cardiac tumors. Metastatic tumors to the heart are much more common than primary tumors, and usually occur in the setting of previously recognized neoplasm. The incidence is especially high in malignant melanoma, carcinoma of the breast and lung, and to a lesser extent, in leukemia and lymphoma. They variably present with dyspnea, acute pericarditis, cardiac tamponade, or the new onset of an ectopic tachyarrhythmia. As with primary tumors, the clinical presentation of metastatic tumors is more closely related to their intracardiac location and size than to the histologic type.

Primary tumors of the heart are rare, and in 75% of cases they are of a benign histologic type. The primary malignant tumors reported are almost always sarcomas.¹³ However, all cardiac tumors have the potential for causing life-threatening complications, and many are now curable by surgery. Therefore, it is important that this diagnosis be considered in MI patients, especially in the absence of recognizable risk factors.

Myxoma, a benign connective-tissue tumor, is the most common primary cardiac tumor in all age groups, accounting for one

Atherosclerosis causes most MIs in the young

TABLE 2

Cardiac myxomas: Clinical presentation of 130 patients (Armed Forces Institute of Pathology series)

PRESENTATION	NO. OF PATIENTS
Findings of mitral valve disease*	57
Embolic phenomenon	36
Incidental finding	16
Tricuspid valve disease*	6
Sudden death	5
Pericarditis	4
Myocardial infarction	3
Pulmonary valve disease	2
Fever of unknown origin	2

*One patient with multiple myxomas had signs and symptoms of both mitral and tricuspid valve disease.

FROM MCALLISTER AND FENOGLIO. TUMORS OF THE CARDIOVASCULAR SYSTEM. FASCICLE 15, SECOND SERIES. ATLAS OF TUMOR PATHOLOGY. WASHINGTON, DC: ARMED FORCES INSTITUTE OF PATHOLOGY SERIES, 1978.

Ask about cocaine use in young patients with angina or panic attacks

third to one half of all cases at autopsy and for approximately 75% of tumors that are treated surgically.¹⁴ It shows no sex preference, although nonfamilial myxomas are seen more often in middle-aged women.

Most sporadic myxomas are solitary and located in the atria, particularly the left atrium, where they arise from the interatrial septum in the vicinity of the fossa ovalis. Sporadic myxomas may also arise in the ventricles or may be found in multiple locations. Most are pedunculated on a fibromuscular stalk and average 5 to 6 cm in diameter.

The most common clinical presentation of cardiac myxoma resembles that of mitral valve disease: either stenosis from tumor prolapse during diastole or regurgitation as a consequence of tumor-induced damage to the valve (TABLE 2).

The valvular obstructive symptoms and signs of atrial myxomas are highly dependent on position and gravity, and thus can be intermittent and sudden in onset. On auscultation, a characteristic low-pitched sound called the "tumor plop" may be audible during early diastole or mid-diastole; this sound is thought to result from the tumor abruptly stopping as it strikes the ventricular wall.

Myxomas can also present with peripheral or pulmonary emboli or systemic symptoms and signs, including fever, weight loss, cachexia, malaise, arthralgias, rash, clubbing, Raynaud phenomenon, anemia or polycythemia, thrombocytopenia or thrombocytosis, an elevated sedimentation rate, and hypergammaglobulinemia. Not surprisingly, myxomas are frequently misdiagnosed as endocarditis, a systemic autoimmune disorder, or as a noncardiac tumor.

Cardiac cysts. Cardiac echinococcosis (hydatid cysts) are rare¹⁵ and account for 0.5% to 2% of all cases of echinococcosis in humans. Most patients with cardiac hydatid cysts have no symptoms; however, sudden death, valvular dysfunction, heart block, and more often, chest pain resulting from episodes of regional pericarditis have been described. Sixty percent of cardiac hydatid cysts are located in the left ventricle, presumably because it has a richer coronary circulation.

Infective endocarditis is not implicated in causing MIs and cardiac masses.

Workup and diagnostic testing

A review of the patient's systems was negative for limb ischemia, subclavian steal (which manifests as syncopal symptoms on exercising), recent weight loss, fevers, night sweats, lymphadenopathy, syncope, or features of a systemic autoimmune disorder. Physical examination revealed no stigmata of vasculitis, embolic phenomenon, splenomegaly, lymphadenopathy, or synovitis. The pulses were equal. The heart sounds were normal, and no "tumor plop," murmurs, or S₃ gallop was noted.

Laboratory evaluation showed normochromic, normocytic anemia with the following values:

- Hemoglobin 10.1 g/dL (normal 12.0–16.0)
- Hematocrit 30.1% (normal 37–47)
- Mean corpuscular volume 86.2 fL (normal 80.0–100.0)
- CK and CK-MB fraction elevated
- Sedimentation rate 118 mm/hr (normal 0–20)
- C-reactive protein 12.3 mg/dL (normal 0–2)
- Antinuclear antibody negative
- *Echinococcus* antibody negative.

A large right-sided cardiac mass



FIGURE 1. The patient's computed tomographic scan of the chest. Arrows show the mass deforming the right atrium and ventricle.

Cardiac myxomas are frequently misdiagnosed as endocarditis, autoimmune disorders, or noncardiac tumors

A computed tomographic scan and magnetic resonance image of the chest revealed a large (6-cm) mass in the right atrioventricular groove, externally invaginating the right atrium and right ventricle and deforming the right coronary artery (RCA). The mass was homogeneous with a well-defined wall and shell-like calcification (FIGURE 1).

Cardiac catheterization showed the RCA to be displaced and compressed by the mass, with compromise of blood flow distally. The distal RCA filled retrogradely from the left coronary artery. Akinesis of the inferior wall was noted, and the left ventricular ejection fraction was similarly estimated to be 50%.

■ PREOPERATIVE DIAGNOSIS

3 What is the most likely preoperative diagnosis?

- ☐ Right atrial myxoma
- ☐ Angiosarcoma
- ☐ Right coronary artery aneurysm
- ☐ Cardiac cyst

Operative notes

A giant coronary aneurysm measuring 6.3 cm by 2.3 cm was resected en bloc from the right atrioventricular groove (FIGURE 2). The

aneurysm had a well-defined capsule, and an organized thrombus was seen intramurally on cut section. On microscopic examination, there was no histologic evidence of vasculitis in the aneurysm.

■ CAUSES OF CORONARY ANEURYSMS

4 All of the following are recognized causes of coronary aneurysms, except which one?

- ☐ Atherosclerosis
- ☐ Kawasaki disease
- ☐ Endovascular infection
- ☐ Syphilis
- ☐ Systemic lupus erythematosus

Coronary artery aneurysms are uncommon, seen in 1.5% to 5% of coronary angiograms, and in 1.4% of young patients at autopsy.^{16–29} In the Coronary Artery Surgery Study (CASS) registry,^{17,18} coronary aneurysms were seen in 978 (4.9%) of 20,087 patients who underwent angiography for suspected coronary artery disease.

The proximal and middle segments of the right coronary artery are most frequently involved, followed in frequency by the proximal left anterior descending and circumflex arteries. Involvement of the left main coronary artery is rare. Men are affected more often than women.

Atherosclerotic or inflammatory coronary aneurysms usually involve more than one coronary artery, in contrast with congenital, traumatic, or dissecting aneurysms. Postulated causes of coronary artery aneurysms are summarized in TABLE 3.

The natural history and prognosis of coronary aneurysms remain obscure, and their management remains a therapeutic dilemma, with published recommendations based on anecdotal experiences.

Patients with coronary aneurysms usually present with symptoms of angina or MI. Occasionally a bruit or murmur, presumably related to turbulent flow, may be heard over the precordium.³⁰ A systolic murmur may also be heard over the precordium. A history of Kawasaki disease or a connective-tissue disorder (eg, Marfan syndrome, Ehlers-Danlos syndrome) may be helpful in suggesting a coro-



nary aneurysm. The possibility of a coronary artery aneurysm should be considered in young patients with ischemic chest pain.

SLE is not a cause of coronary aneurysms.

■ KAWASAKI DISEASE

The patient recalled being diagnosed with scarlet fever as a young child. Her mother said that at age 4, the patient had a prolonged febrile illness with a sore throat, cervical lymphadenopathy, rash, and myalgias. Desquamation of the skin of the hands and feet occurred at the end of the patient's clinical illness.

Kawasaki disease is an acute febrile illness of childhood and is the primary cause of acquired pediatric heart disease in children in the United States and Japan.³¹ It is now known to be a systemic vasculitis involving predominantly small and medium-sized muscular arteries, especially the coronary arteries. Morbidity and mortality from the disease are most often caused by cardiac sequelae, predominantly coronary aneurysm formation with subsequent coronary thrombosis or embolism or both.

Acute treatment of Kawasaki disease with intravenous immune globulin is predicated on preventing formation of coronary aneurysms.^{32,33} A causative organism or toxin for Kawasaki disease has not been identified.

Eighty percent of cases of Kawasaki disease occur in children younger than 5 years.³⁴ The incidence is between 6 and 15 cases per 100,000 children in this group, with Asian-Americans proportionately overrepresented and white Americans underrepresented.

Cardiac abnormalities in Kawasaki disease

Cardiac abnormalities are seen in approximately 30% of cases of Kawasaki disease during the acute stage. Myocarditis is common, and congestive heart failure, pericardial effusions, and atrial or ventricular arrhythmias can occur. Mitral regurgitation, usually mild, occurs in approximately 30% of patients.

Coronary artery lesions are responsible for most of the morbidity and mortality of Kawasaki disease. Before immune globulin came into widespread use, aneurysms devel-

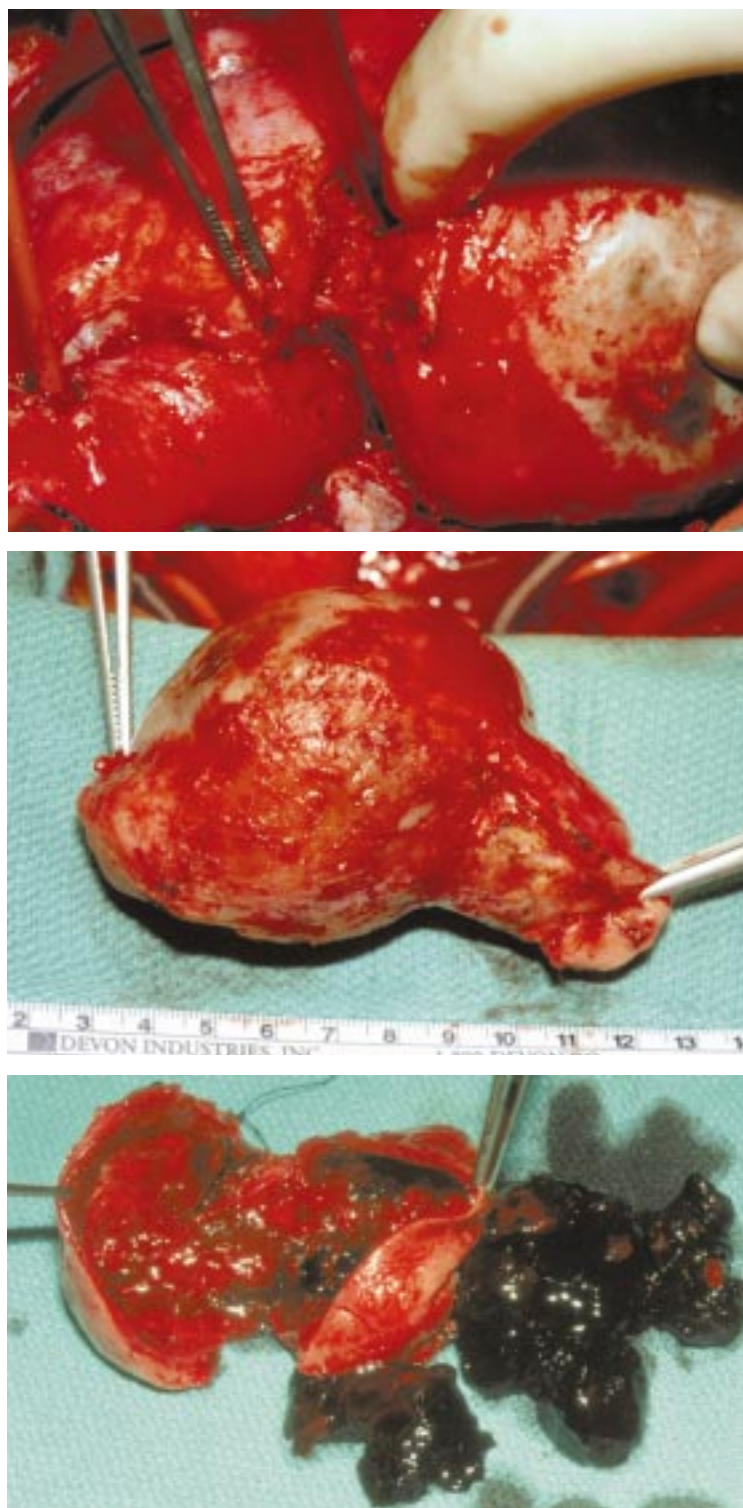


FIGURE 2. Top, a giant coronary aneurysm measuring 6.3 cm by 2.3 cm in the right atrioventricular groove. Middle, the resected aneurysm en bloc. Bottom, the aneurysm shows an organized thrombus and a well-defined vascular capsule on cut section.

**TABLE 3****Postulated causes of coronary artery aneurysms**

Atherosclerosis
Kawasaki disease
Congenital
Coronary angioplasty
Arteritis (polyarteritis nodosa, systemic lupus erythematosus, syphilis, Takayasu)
Mycotic
Dissection
Marfan syndrome, Ehlers-Danlos syndrome
Cerebrotendinous xanthomatosis
Quartan malaria³⁹
Neurofibromatosis

oped in approximately 15% to 25% of patients, but now occur in fewer than 10%.³⁵ Aneurysms usually appear from 1 to 4 weeks after the onset of fever; it is rare to detect new lesions after 6 weeks. Aneurysms are most easily detected by transthoracic two-dimensional echocardiography. If MI occurs, it is likely to be in the first year, with 40% of MIs occurring in the first 3 months of illness.

Regression of aneurysms

The natural history, or fate, of the coronary aneurysm is the important issue in Kawasaki disease. Most ectatic (dilated) coronary lesions and small aneurysms regress in size. Moderate aneurysms may remain unchanged, regress, or progress to stenosis or obstruction. Giant aneurysms rarely regress.

In a multivariate analysis,³⁶ regression of an aneurysm was significantly related to the initial size of the aneurysm, initial treatment, and gender. By discrimination analysis, the risk factors for coronary aneurysms developing into ischemic heart disease included aneurysm size greater than 8 mm and aneurysm shape. Coronary aneurysms that developed in patients older than 2 years were also less likely to regress. Regression was significantly related to the severity of the coronary artery lesions, initial treatment, and gender. Girls had a higher regression rate than boys. In children treated with salicylates alone, 50% of the lesions did not regress by 5 years; those treated

with immune globulin had an 85% regression in 5 years.

However, there are case reports of young adults who suffer MIs more than a decade after their initial disease, and others with coronary artery aneurysms who were not known to have Kawasaki disease as children.^{37,38} In one study,³⁷ 594 patients with Kawasaki disease were followed angiographically for 10 to 21 years. Coronary stenosis developed in 28 patients; 11 patients had MIs, and 5 died. No regression was seen in 26 patients who developed giant coronary aneurysms. The 448 patients with normal findings on the first angiogram never developed subsequent abnormal cardiac findings.

SEARCH FOR CONTRIBUTING FACTORS IN MI IN THE YOUNG

MI in young patients is relatively infrequent. Although atherosclerotic disease is responsible for most cases, secondary causes of MI are responsible for one fifth of reported cases. Cigarette smoking is the most common modifiable risk factor; lipid abnormalities are also important. When no risk factors for atherosclerosis are present, a careful search for other contributing factors such as vasculitis, coronary vasospasm, cardiac masses, or hypercoagulable states is warranted.

As more children who survive Kawasaki disease become adults, the proportion of cardiac events related to aneurysm formation is likely to increase. All young patients who present with symptoms of myocardial ischemia should be questioned about and screened for cocaine use and a childhood history of Kawasaki disease. Regardless of the underlying cause, aggressive secondary prevention should remain the main focus of therapy, with smoking cessation and lipid-lowering therapy.

FINAL DIAGNOSIS

The final diagnosis of this patient was acute MI secondary to thrombosis of a giant right coronary artery aneurysm as a sequel of childhood Kawasaki disease.

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Although uncommon, coronary aneurysms can cause angina or MI



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Kawasaki disease is the primary cause of acquired heart disease in children