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Sudden Death Caused by Coronary Artery Aneurysms: A Late Complication of Kawasaki Disease

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ABSTRACT: The authors describe three cases (two blacks and one Latin American) of sudden death caused by late complications of Kawasaki disease (mucocutaneous lymph node syndrome). At autopsy each heart contained multiple coronary artery aneurysms with luminal stenosis caused by intimal hyperplasia and thrombi. Although virtually all fatal cases of Kawasaki disease occur within six months of the onset of symptoms, there have been other reported deaths up to 14 years after the acute illness. The coronary artery aneurysms of Kawasaki disease may persist and cause death years after the acute illness.

KEYWORDS: pathology and biology, cardiovascular system, symposium, Kawasaki disease, mucocutaneous lymph node syndrome, coronary aneurysm, coronary arteritis, sudden death

Kawasaki disease is an acute febrile illness of childhood which may be complicated by coronary arteritis with subsequent aneurysm formation, of which about one half of the cases resolve with time. Death occurs in 1 to 2% of cases due to myocardial ischemia caused by thrombosis or rupture of aneurysms of the coronary arteries and other cardiac complications such as myocarditis [*1,2*]. Occasionally, the disease can be fatal a long interval after the initial presentation. We describe three cases, two young adults and a child, who died suddenly of coronary artery stenosis or occluded coronary artery aneurysms years after a febrile illness consistent with atypical (two cases) and typical (one case) Kawasaki disease. The young adults were black and the child was Latin American. Kawasaki disease occurs less frequently in these racial groups than in Orientals.

Cases

Case 1

A 17-year-old black male collapsed suddenly after lifting weights during a baseball practice. He was found to be pulseless and unresponsive at the scene by emergency medical personnel and was transported to a hospital. Attempts at cardiopulmonary resuscitation (CPR) failed.

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At autopsy, the body was that of a heavyset (180-cm, 135-kg) 17-year-old black male. Both lungs were edematous and congested. The 540-g heart contained a large calcified fusiform aneurysm of the left main coronary artery (LMCA) and proximal left anterior descending (LAD) coronary artery (Fig. 1). The aneurysm measured 2.2 cm in diameter and extended 2.8 cm along the course of the LMCA from the left coronary ostium. It contained a thrombus which occluded both the proximal left anterior descending and left circumflex arteries (Fig. 2). The right coronary and left anterior descending coronary arteries also had proximal aneurysmal dilatations. Microscopic examination revealed that they contained multiple lumens of recanalized old occlusive thrombi with fibrous intimal thickening and fibrosis (Fig. 3). The internal and external elastic lamina were disrupted (Fig. 4). No evidence of myocardial infarction was found.

A review of his past medical history showed that this subject had had an illness at age 8, presenting as left posterior cervical adenopathy, bilateral conjunctivitis, gingivitis, and arthralgias of the wrists followed by a fever of 104°F (40°C), which lasted for an undocumented duration. A diagnosis of Vincent's angina was made, and the patient was treated with sulfonamide eye drops; the recovery was apparently uneventful.

Case 2

A 19-year-old black male collapsed and died after a two-mile run. His past history included a three-week illness at age 4, which was characterized by stomach pain, fever, pharyngitis, otitis, photophobia, myalgias, cervical lymphadenopathy, and a rash which began in the second week in the inguinal area and spread throughout the body. The rash became desquamative with blister-like lesions of the fingertips. The laboratory findings included a complete blood count showing a white blood count of 14 900 with 76% segmented neutrophils, 2% eosinophils, 20% lymphocytes, and 1% atypical lymphocytes. A monospot test was negative; heterophile antibody testing was positive at a dilution of 1:56; and the serum glutamic-oxalacetic transaminase was 40 units. Febrile agglutinins

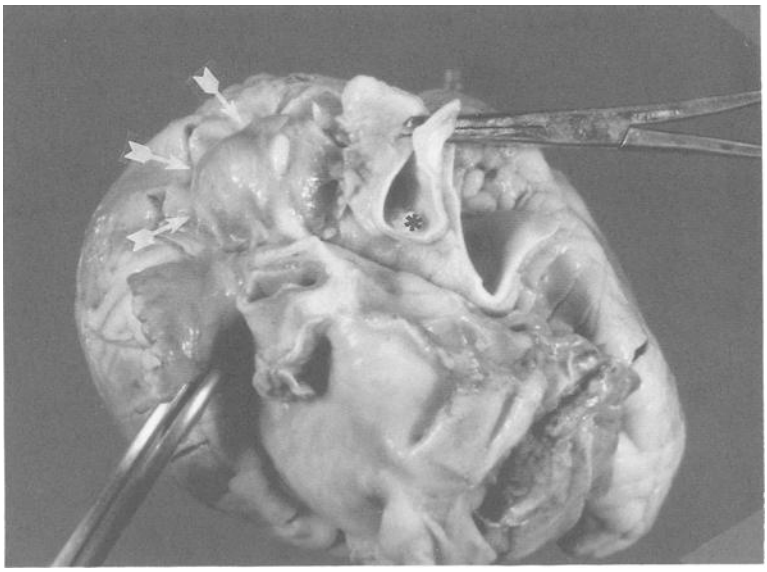

FIG. 1—*Fusiform aneurysm* (arrows) *of the left main and left anterior descending coronary arteries, Case 1. The asterisk indicates the aorta.*

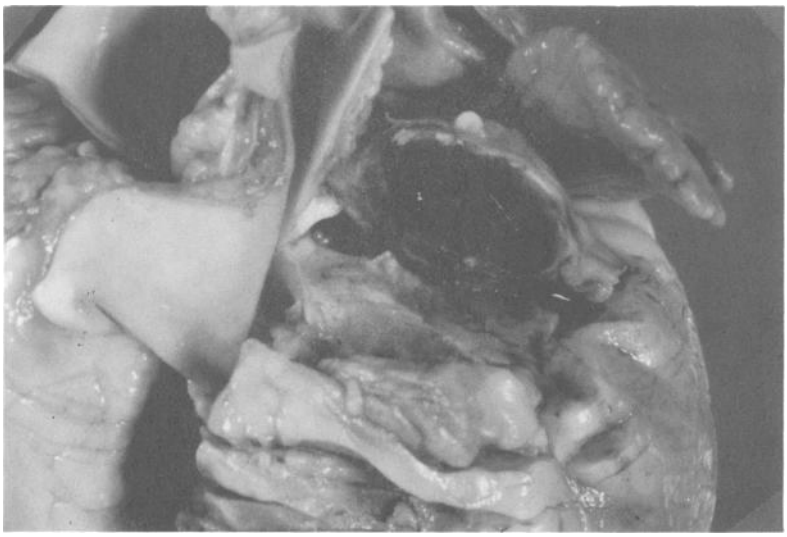

FIG. 2—*Cross section of thrombus-filled aneurysm, Case 1.*

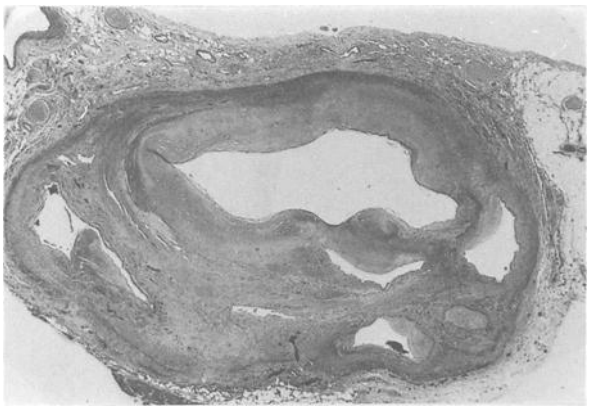

FIG. 3—*Left anterior descending coronary artery distal to the aneurysm, Case 1. There are multiple lumina. (Magnification, ×1; Movat pentachrome.)*

and leptospirosis serology were negative and the patient was diagnosed as having a viral illness. He was treated with penicillin G, aspirin, and acetaminophen.

At autopsy, the body was muscular, with a weight of 92 kg and measuring 183 cm in height. The principal autopsy finding involved the heart, which showed an extensive healed myocardial infarct involving the anterior interventricular septum and the anterior and lateral portions of the left ventricular wall. In addition, there were three coronary artery aneurysms. Two of these involved the right coronary artery, the more proximal one measuring 1.3 by 1.0 cm and located just distal to the ostium. The other was 3 cm from the ostium and measured 0.9 cm in diameter (Fig. 5). Both were occluded, the more proximal with calcified debris and the more distal by metaplastic bone marrow. The third aneurysm involved the left main coronary artery, with the left anterior descending artery taking off from the aneurysmal wall. This aneurysm, which measured 0.9 by 1.1 cm, showed calcification of the wall without luminal narrowing (Fig. 6).

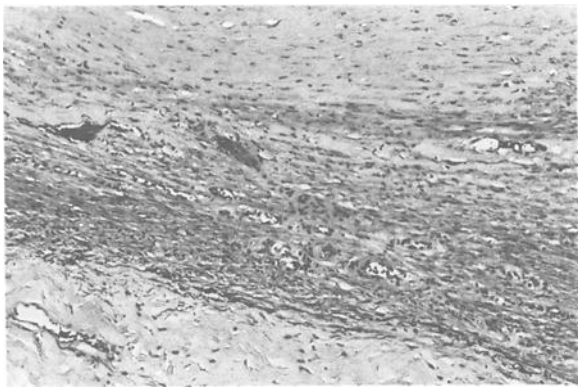

FIG. 4—*Left anterior descending coronary artery showing disruption of external elastic lamina* (bottom) *and the absence of internal elastic lamina, Case 1. There is intimal fibrosis at the top. Magnification, ×100; Movat pentachrome.)*

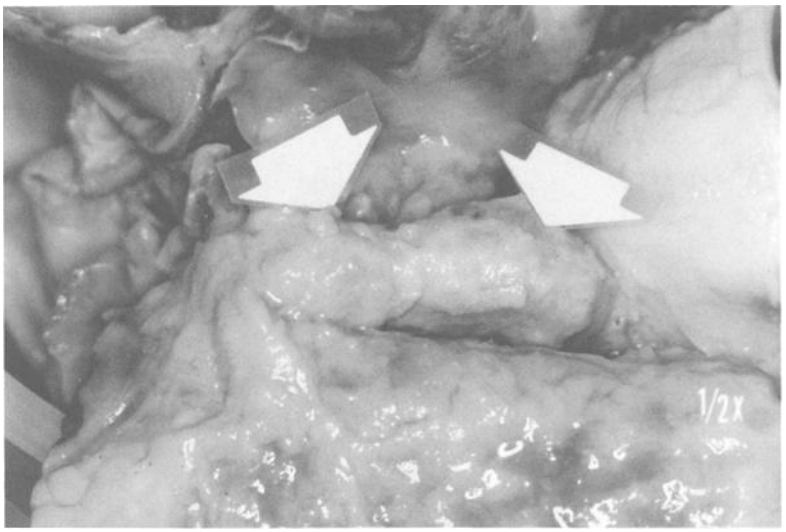

FIG. 5—*Right coronary artery showing two aneurysms, indicated by arrows, Case 2.*

Case 3

This 4-year-old Latin American male child, previously in good health, suddenly became weak, vomited, and was taken to a local hospital emergency room. He died 5 h after arrival. He was the product of a normal-term pregnancy, with an uncomplicated spontaneous vaginal delivery. At age 13 months he had had a febrile illness lasting five days, an erythematous macular rash, pharyngitis, diarrhea, and dull tympanic membranes. Twenty days later his fever was intermittent but the diarrhea and rash had cleared. His erythrocyte sedimentation rate was 125 mm/h (Westergren). A chest X-ray showed a probable enlarged cardiac silhouette. Febrile agglutinins, rheumatoid factor, and antinuclear antibodies were absent. Five weeks after his initial illness, an electrocardiogram was normal. Two months after his initial presentation, chest X-rays revealed the heart to be at the upper limit of normal size. He was lost to follow-up until death.

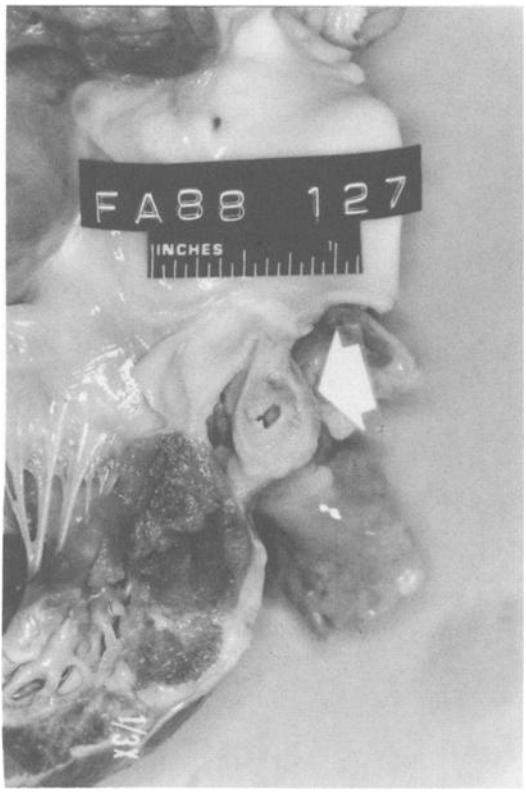

FIG. 6—*Cross section of the left anterior descending coronary artery aneurysm, Case 2.*

Pertinent autopsy findings included a mildly enlarged 140-g heart with diffuse narrowing estimated to be 95 to 99% of the left anterior descending, left circumflex, and right coronary arteries. The left main and proximal left anterior descending coronary arteries (Fig. 7) contained aneurysms measuring 0.6 cm each. The LAD immediately distal to the aneurysm measured 0.3 cm. The posterior left ventricle contained a 7-mm-wide area of fibrosis extending from the apex halfway to the base. Additional small foci of fibrosis were present in the posterior left ventricle at the base. The anterior wall of the left ventricle contained a 4-mm-wide area of fibrosis extending from the base halfway to the apex.

Microscopically, the coronary artery lumina were narrowed by intimal fibrosis (Fig. 8), which was focally calcified. Some narrowed arteries were recanalized. The myocardium contained extensive acute infarct manifested by coagulation necrosis with contraction bands and a neutrophilic infiltrate, in addition to the old infarct observed grossly.

Discussion

The autopsy findings were those of healed arteritis and aneurysmal dilatation of the coronary arteries. Two of the patients had myocardial infarction. In each patient there was a childhood illness consistent with atypical Kawasaki disease (Cases 1 and 3) or typical Kawasaki disease (Case 2). No patient was symptomatic after the earlier acute illness up to his death.

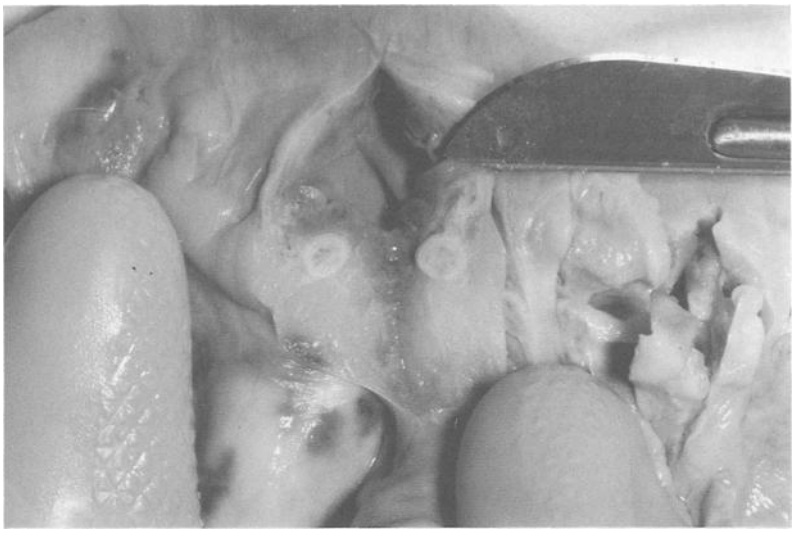

FIG. 7—*Cross section of the aneurysm of the left anterior descending coronary artery, Case 3.*

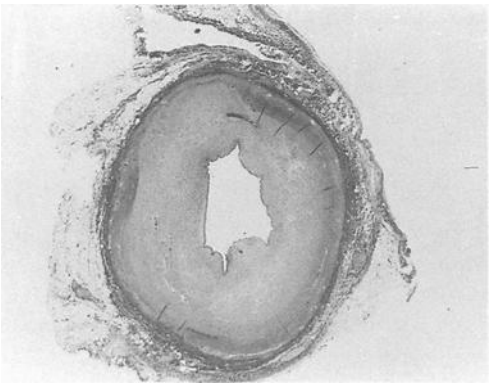

FIG. 8—*Left anterior descending coronary artery with luminal narrowing caused by intimal hyperplasia, Case 3. (Magnification, ×1; Verhoeff VanGieson/Masson trichrome.)*

Kawasaki disease, first described in Japan in 1967 as mucocutaneous lymph node syndrome (MLNS) [3], has an incidence of 0.59 cases per 100 000 children less than five years old in the United States, with 50% of the cases being reported in children less than two years old [4]. The male to female ratio is 1.6:1. Its peak incidence is between February and May, and it affects racial groups in the following order: Orientals, Blacks, Hispanics, and Caucasians. The etiology of Kawasaki disease is unknown. Because of the seasonal variation and reported epidemics, a transmissible agent is suspected.

In the acute phase, Kawasaki disease is characterized by (1) an unexplained febrile illness lasting for five or more days; (2) bilateral conjunctivitis; (3) mucous membrane changes such as injected or fissured lips, "strawberry" tongue, or pharyngitis; (4) erythema of the palms or soles, edema of the hands or feet, or desquamation of the fingers and toes; (5) a rash, which is usually scarletiniform; and (6) cervical adenopathy. Di-

agnosis of typical Kawasaki disease requires that five of the six criteria be present and 90% of all cases fit this definition [*4–6*]. In the remaining 10%, fewer than five of the criteria are present [*3,7,8*]—these cases are considered to be atypical Kawasaki disease. Atypical cases usually present as an unexplained febrile illness. About half have the oral mucosal changes listed above and desquamation of the fingers and toes. Recurrent episodes of Kawasaki disease can occur, and some of these episodes may be subclinical [*6*]. Other findings that have been reported include aseptic meningitis with pleocytosis, anemia, myocarditis, pericarditis, diarrhea, and mild jaundice [*6,9*].

After the initial acute illness that lasts for one to two weeks, the disease progresses into a subacute phase. During this time, 15 to 20% of the patients develop coronary aneurysms and 1 to 2% die from myocardial infarcts. Seventy percent of the deaths occur 15 to 45 days after the onset of fever and virtually all within four to six months [*10*].

The convalescent stage begins approximately 25 days after the onset of the disease and lasts until the erythrocyte sedimentation rate (ESR) returns to normal. Half of the coronary aneurysms will resolve, while the remainder are at high risk of causing sudden cardiac death [*1*]. Several factors are associated with the regression of the aneurysms. Fusiform aneurysms will resolve more frequently than saccular aneurysms, as will those in younger patients [*11*]. It is also noted that distal aneurysms will resolve faster than proximal aneurysms, probably because most distal aneurysms are fusiform. Only one out of six aneurysms of the LMCA will resolve [*2*]. Resolution occurs over several months [*11*].

Aneurysms occur most often in the coronary arteries but are also seen in other vessels, most commonly the iliac arteries [*12*]. Two thirds of the patients have a single coronary aneurysm by echocardiography [*11*]. The aneurysms tend to be in the proximal coronary arteries and are saccular [*11*]. Microscopically, Kawasaki disease is a vasculitis of the small and medium-sized arteries. In the first stage there is a neutrophilic and lymphocytic infiltrate of the adventitia and intima. The infiltrate then extends into the media, resulting in the formation of aneurysms. Resolution is characterized by intimal hyperplasia and luminal stenosis, often with multiple microscopic neolumina, and medial and adventitial fibrosis [*11,13*].

While no single diagnostic laboratory test is specific for Kawasaki disease, several abnormalities have been reported [*4,5,9*]. These include elevated ESR, thrombocytosis, and leucocytosis with left shift. The serum often has an increased C reactive protein and alpha-2 globulin with hypoalbuminemia. Immunoglobulins and complement levels may be elevated along the transaminase levels. The anti-streptolysin O test is negative. Proteinuria, pyuria, and microscopic hematuria may occur. The formation of aneurysms may be related to the level of beta-thromboglobulin in the serum during the first three weeks of illness. Burns et al. [*14*] found that those patients with aneurysms had an elevated beta-thromboglobulin compared with patients who did not develop aneurysms. This test may be useful in deciding which patients need echocardiography or cardiac catheterization.

Traditionally, aneurysms have been identified by echocardiography, which can detect aneurysms larger than 1 cm but which frequently fails to detect aneurysms of the right coronary artery. With angiography, aneurysms may not be detected because of partial filling of the lumen by intimal thickening or organizing thrombi or both, falsely suggesting resolution [*15*]. More recently, magnetic resonance imaging [*16*] and ultrafast computerized tomography [*17*] have been proposed as noninvasive methods for accurate diagnosis of Kawasaki-disease-associated aneurysms. Nakano et al. suggest that large-dose immunoglobulin therapy early in the course of the disease may prevent aneurysm formation [*18*]. Steroid treatment should be avoided as there is evidence that it may increase the occurrence of aneurysms [*19*]. Coronary aneurysms may be treated with coronary bypass grafting [*2,12*].

Five other patients reported in the literature, ranging in age from 9 to 17 years, have

died suddenly from coronary artery aneurysms caused by Kawasaki disease [*15,20–23*]. The time between the first presentation of Kawasaki disease and death ranged from 2 [*23*] to 14 years [*20*]. In four cases [*15,20,21,23*], death followed vigorous activity and in the case reported by Kegel et al. [*22*], the patient experienced vomiting and chest pain after a soccer game, was admitted to the hospital, and was found dead in his hospital bed at least one day (interval not specified) after admission. Four patients had old myocardial infarction and the patient reported by Quam and associates [*21*] had an hours-old infarct as well. McCowen and Henderson failed to mention whether a myocardial infarct was present [*23*]. In each instance, the aneurysms had luminal narrowing caused by intimal hyperplasia and thrombus.

In their review of 26 cases of coronary artery aneurysms following acute episodes of Kawasaki disease, Tanaka et al. [*24*] reported a 9-year old who died 8 years after the acute phase, but the circumstances of the fatal collapse and the presence of myocardial infarct were not mentioned. Yanagisawa [*25*] described a 21-month-old child with coronary artery aneurysm who died of congestive heart failure due to old myocardial infarct 15 months after the acute phase of Kawasaki disease.

The diagnosis of coronary artery aneurysms occurring years after the acute phase of Kawasaki disease requires a high index of suspicion. There are no specific serologic tests to indicate prior Kawasaki disease, and the diagnosis of coronary artery aneurysms can only be made radiologically. Many cases of "congenital coronary artery aneurysms," usually occurring in the proximal portion of the vessel, are probably late sequelae of Kawasaki disease. These cases demonstrate that, in rare cases, coronary artery aneurysms may become manifest years after the acute illness as sudden cardiac death.

Addendum

Another report of a coronary artery aneurysm as a late sequela to an episode of atypical Kawasaki disease has come to our attention [*26*]. The patient was a 23-year-old Japanese male who died during a karate match 17 years after a febrile disease that fulfilled the criteria for atypical Kawasaki disease.

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