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## Giant Coronary Aneurysms in a Young Adult Patient with Kawasaki Disease

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**Kawasaki disease is an acute, self-limited vasculitis of childhood and the principal cause of acquired heart disease in children in several parts of the world. Its major morbidity and mortality is related to the development of coronary aneurysms. The long-term impact of this disease in adults is not known, however, clinically silent coronary artery aneurysms may be recognized after a sudden cardiac event, even death. We report a case of Kawasaki disease in a young**

**asymptomatic Puerto Rican man who presented to our Adult Cardiology Clinic with multiple giant coronary aneurysms. A brief review of the epidemiology, etiology, pathophysiology, clinical features, therapeutic modalities, prognosis and complications of this condition is also included.**

*Key words: Kawasaki disease, Giant coronary aneurysms, Therapy, Coronary revascularization criteria*

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**K**awasaki disease is an acute, self-limited vasculitis of childhood, but with the possibility of causing long-term, serious cardiac sequelae such as, coronary artery stenosis and coronary aneurysms. Myocardial infarction from thrombus development in giant coronary aneurysms constitutes its major dreaded complication. Infrequently sudden death may also result from myocarditis, coronary ischemia or rupture of coronary aneurysms (1).

### Case Report

A 19-year-old Puerto Rican man was referred to our Adult Cardiology Clinic late in 2007 for further evaluation and follow up. His past medical history was noteworthy for a previous hospitalization (7 years earlier) to the San Juan University Pediatrics Hospital characterized by high fever, cervical lymphadenopathy and desquamation of the hands. During the hospitalization he was treated with aspirin and intravenous antibiotics. He did not receive intravenous gamma globulin (IVIG), as it was considered that Kawasaki disease was not present. After discharge, he was kept under periodic ambulatory follow up at the Cardiology Pediatrics Clinic on aspirin therapy.

He consistently denied chest pain, shortness of breath or palpitations. The general physical examination was unremarkable. The blood pressure and heart rate were normal. There were no murmurs or gallops. The peripheral pulses were strong bilaterally at both the upper and lower extremities.

During serial visits, a two-dimensional echocardiogram suggested the presence of coronary artery aneurysms, so a chest computed tomographic scan with intravenous contrast was performed on December 2007. The study disclosed aneurysmal dilatation of the proximal and mid segments of the right coronary artery (RCA), along with large, proximal fibrocalcific plaques resulting in high grade luminal obstruction. The largest vessel diameter measured 20.0 mm; post-stenotic dilation of the distal segment of the RCA (measuring 12 mm in diameter) was also described. Additional description included aneurysmal dilatation of the left main coronary artery (8 mm in diameter proximal to its bifurcation) and of the proximal segment of the left anterior descending coronary artery (LAD), which measured 6.4 mm in diameter. Subsequent coronary angiography performed on January 2008 showed aneurysmal dilatation of the left main coronary artery (8.02 mm in diameter proximal to its bifurcation) with extension into the LAD (maximum diameter of 5.84 mm) (Figure 1). The RCA also showed a proximal aneurysm (9.46 mm in diameter) and an aneurysm in its middle third (11.01 mm in diameter) without stenosis of the connecting segments (Figure 2). No evidence of obstruction or thrombus were detected.

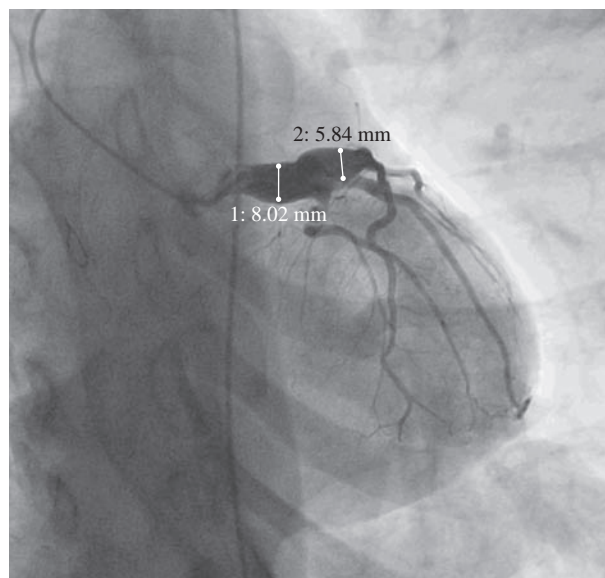
Based on this patient's past medical history and the above angiographic findings a diagnosis of Kawasaki disease was made. During follow up at our Adult Cardiology

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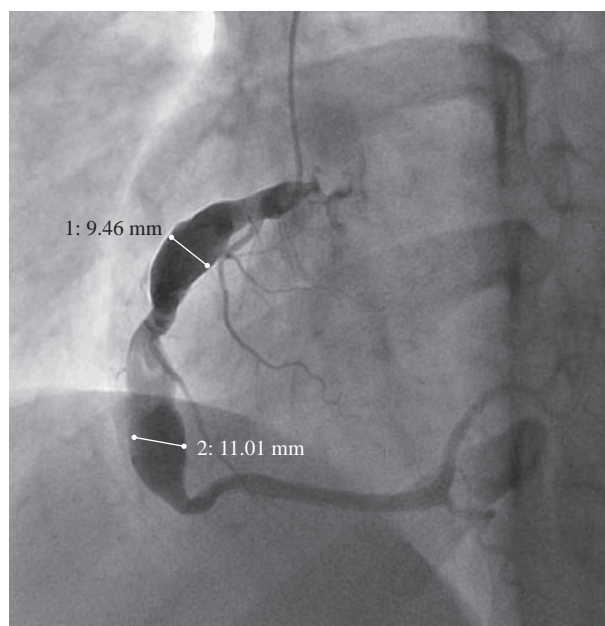
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Ambulatory Clinic the patient has been maintained on low dose aspirin and oral warfarin anticoagulation therapy, with a goal of maintaining his International Normalized Ratio (INR) between 2.0 and 2.5. He is to remain on that therapeutic regimen indefinitely. He has persisted totally asymptomatic up to the time of this report.



**Figure 1.** Left coronary angiogram showing a 8.02 mm in diameter aneurysm in the left main coronary artery and a 5.84 mm in diameter aneurysm in the proximal left anterior descending coronary artery.



**Figure 2.** Right coronary angiogram. Proximal (9.46 mm in diameter) and middle third (11.01 mm in diameter) aneurysms without stenosis of the connecting segments are depicted.

## Discussion

### Epidemiology

Kawasaki disease is an acute, systemic, febrile illness of childhood with worldwide occurrence but higher prevalence in the Asian population. It has become the principal cause of acquired heart disease of children in Japan and the United States. In this latter country, around 3,500 cases of Kawasaki disease are reported annually, with a peak incidence in children younger than 2 years of age. It is rarely found in children beyond 8 years, as described in the patient presented in this case report (2).

### Etiology and Pathophysiology

Even though fever, adenopathy, conjunctivitis and geographical clustering suggest the possibility of an infectious etiology, no such agent has ever been identified (3). The disease is characterized by two phases: an acute phase which lasts from 1 to 2 weeks and a chronic (“convalescent”) phase. Most cases usually resolve spontaneously after few weeks. The most prominent pathologic characteristic of Kawasaki disease is an acute systemic vasculitis with evidence of widespread immunoinflammatory activation (4). Lesions in the coronary arteries usually develop early during the acute phase and infrequently more than 4 weeks after onset of the disease. Early lesions are characterized by prominent endothelial cell edema, proliferation, necrosis and the adhesion of polymorphonuclear cells to the endothelium. This process is usually accompanied by noticeable immune activation with increased levels of various cytokines, including TNF- $\alpha$ , and IL-1, IL-2, IL-6, IL-8 and IFN- $\alpha$ , CD4 and CD8 cytotoxic cells, polyclonal hypergammaglobulinemia and circulating IgG and IgM immune complexes (5-6).

### Clinical Features

The major clinical features of Kawasaki disease are those comprised in the case definition guidelines of the Centers for Disease Control and Prevention, and include fever (lasting for more than 5 days and without any other explanation), plus at least four of the following: rash, oral mucositis, conjunctivitis, cervical lymphadenopathy and skin desquamation. The diagnosis requires the presence of at least 5 of these features, or of 4, if accompanied by the presence of coronary aneurysms (7). Frequent laboratory findings include leukocytosis, elevation of the erythrocyte sedimentation rate, thrombocytosis and increased C-reactive protein levels and serum transaminases. No specific, single serological diagnostic test is included in the CDC diagnostic guidelines. The acute illness is usually self-limited, typically 4 to 6 weeks in duration.

### **Cardiac findings**

Myocarditis frequently occurs to some extent during the acute phase of the disease but usually resolves completely and has not been found to foretell future involvement of the coronary arteries (8). Physical and clinical findings may include S3 or S4 gallops, nonspecific ST-T changes or low voltage on the electrocardiogram, cardiomegaly on chest radiography and small pericardial effusions and depressed left ventricular systolic function on the echocardiogram. However, long-term impairment of left ventricular systolic function seldom occurs in the absence of coronary artery disease (9). Involvement of the aortic and mitral valves rarely occurs, and if it does, it is a usually clinically benign affair which regresses spontaneously (10).

### **Coronary Artery Aneurysms**

Coronary artery complications may occur in up to 10 to 20% of patients during the acute stage, of which approximately 4% progress to ischemic heart disease (11). Factors related to aneurysmal formation include prolonged high fever, persistently elevated erythrocyte sedimentation rate, markedly elevated white blood cell counts and anemia. However, none of those factors has been found totally predictive of aneurysmal development (12). The aneurysms largely occur in the proximal segments and at bifurcations of the coronary arteries, often affect multiple vessels and are usually present in around 90% of fatal cases. Development of aneurysms may also occur in the renal, axillary or iliac arteries.

Coronary artery aneurysms are usually diagnosed with two-dimensional echocardiography. This diagnostic method has a reported sensitivity and specificity of 90 to 95% for the detection of proximal aneurysms, respectively (13). Serial echocardiography is warranted whenever an aneurysm is found. Coronary angiography is considered essential only when coronary artery aneurysms are identified. Aneurysms are considered small if their maximal internal diameter is less than 3 mm, medium size if from 3 to 6 mm, large if more than 6 mm and giant if they exceed 8 mm. Small or medium size aneurysms may undergo regression, however, abnormal vascular wall morphology and vascular dysfunction may persist. In contrast, giant aneurysms may lead to thrombus formation or stenosis. Half to two-thirds of the aneurysms disappear spontaneously and in around 50% of the patients total disappearance of aneurysms is confirmed with echocardiography or coronary angiography within one year after onset of the disease (14-15).

### **Prognosis, morbidity and mortality**

It is frequently observed that patients with Kawasaki disease who exhibit coronary aneurysms remain

asymptomatic, as in the patient under consideration in this case report. Many of these patients have normal electrocardiographic and stress tests findings and remain at low risk for subsequent myocardial infarction or sudden death. However, occasionally aneurysms are persistent and lead to occlusive coronary disease increasing the risk for myocardial infarction or even sudden death. As myocardial infarction can occur early or late after the acute phase, patients must be carefully followed into adulthood and should be counseled on avoiding traditional atherosclerotic risk factors and the adoption of healthy living styles (16).

In general, giant coronary artery aneurysms are characterized by a poor prognosis. These larger lesions do not usually regress and frequently lead to ischemic heart disease. The present overall mortality rate of Kawasaki disease in children is less than 1%.

### **Treatment**

The main goal of treatment of Kawasaki disease in its acute stage is the control of the acute inflammatory process and the prevention of serious cardiovascular complications, such as coronary artery disease. At present the recommended standard treatment at this phase of the disease is a single infusion of intravenous gammaglobulin (IVIG) (2 g/kg), followed by low-dose aspirin therapy. This regimen has been found to more effectively accelerate the resolution of the systemic inflammatory process (17). An additional recommendation is continuation of aspirin therapy until the laboratory markers for acute inflammation return to normal, unless coronary artery abnormalities are detected by echocardiography. Diffuse dilatation of the coronary arteries may be detected by echocardiography in about 50% of children around the 10<sup>th</sup> day of illness. A 20 to 25 % incidence of coronary aneurysms have been reported by the 11<sup>th</sup> to 12<sup>th</sup> day of illness in untreated or those just treated with aspirin (18). In contrast, a 4 to 5% incidence has been reported in those that receive combined therapy within the first 10 days of illness. Furthermore, patients who receive IVIG rarely develop giant coronary aneurysms, which are the lesions associated with higher risk for future ischemic heart disease. Since up to 80% of IVIG recipients may never develop coronary artery aneurysms, the identification of patients who remain at higher risk for coronary disease is fundamental.

The American Heart Association has issued recommendations for long-term follow-up of patients with Kawasaki disease with coronary aneurysms (19). These include antiplatelet therapy with aspirin, dipyridamole and clopidogrel, either alone or in combination. Despite these guidelines, no definitive clinical data is available to show that the combined use of two antiplatelet drugs is superior to aspirin alone. Clinical indications for more potent antiplatelet

agents, such as the glycoprotein IIb/IIIa inhibitors, are uncertain at present. Studies have proven that the widespread use of aspirin is the single most effective factor that has reduced the mortality of Kawasaki disease from almost 2% in the past to the current level of < 0.5 % (19).

As patients with giant coronary aneurysms may form an occlusive thrombus despite the use of antiplatelet drugs, anticoagulation therapy is also recommended in those with multiple, giant aneurysms or obstructive lesions. Warfarin doses are to be regulated to keep the INR between 2.0 and 2.5, combined with low dose aspirin. This course of therapy is continued unless the aneurysms regress to a diameter of less than 6 mm. Evaluation by stress testing during adolescence in order to detect silent ischemia and as an aid to guide further therapy is also strongly recommended (19).

### **Revascularization**

Coronary revascularization either percutaneous (PCI) or surgical (CABG), has been employed in patients with Kawasaki disease and evidence of coronary ischemia (16). Although, the use of percutaneous coronary interventions (PCI) may be effective as short-term therapy for coronary stenoses, its long-term efficacy requires further verification. Moreover, this therapeutic modality is not recommended for ostial or long segmental lesions. The experience with drug-eluting stents is still limited.

The experience with CABG is greater than that with PCI in Kawasaki disease (20). Arterial grafts have shown greater longevity than vein grafts and have been demonstrated to grow in caliber and length in parallel with the somatic growth of the child (21). Although controversy exists regarding the indications for CABG in Kawasaki disease, most agree on the need for CABG in the presence of severe obstruction of the left main coronary artery or high-grade obstruction in at least two of the three major coronary arteries (22). The presence of high-grade obstruction in the proximal LAD is also an acceptable indication. Other indications include ischemic symptoms and signs, progressive enlargement of an aneurysm and giant aneurysms with or without stenosis, when ischemia is detected.

Heart transplantation has been rarely employed in patients with Kawasaki disease and there is limited published data regarding this matter (23). An international review identified only 13 reported cases. Indications for the procedure include severe myocardial dysfunction, severe ventricular arrhythmias and severe distal multivessel coronary artery disease not amenable to CABG.

### **Risk stratification for coronary artery disease (CAD)**

As Kawasaki disease is considered a risk factor for adult-onset CAD, risk stratification is very important

after resolution of the acute phase. The magnitude of the risk is related to the severity of coronary artery involvement and the presence of ongoing inflammation (24). Serial evaluation of the distribution and size of coronary artery aneurysms is essential for risk stratification and therapeutic management. Transthoracic echocardiography (TTE) is usually sufficient for that purpose initially. However, as coronary artery visualization becomes more difficult as children grow, CT angiography or coronary magnetic resonance angiography (MRA) are being evaluated as non invasive diagnostic alternatives when image quality by TTE is inadequate, thus reducing the need for serial x-ray coronary angiography in these patients (25-26).

Some studies have indicated long-term alterations in lipid metabolism that persist past the clinical resolution of the disease (27). CAD risk assessment is to be individualized but it is advisable that all patients with history of Kawasaki disease be counseled on adoption of healthy lifestyles, with particular emphasis on regular physical activity and diet programs. Further considerations for more aggressive interventions are to be taken according to family history, extent of coronary involvement, the presence of markers of inflammation and of traditional and life-habits risk factors (28-29).

### **Conclusion**

Kawasaki disease is generally a self-limited systemic vasculitis of childhood. Due to its predilection for affecting the coronary vasculature it may be recognized in adulthood, with either clinically silent multiple, giant coronary aneurysms (as in the case described in this report) or with a sudden catastrophic cardiac event. Long-term treatment with antiplatelet agents and oral anticoagulation, along with close monitoring for complications, is advised for adult patients with clinically silent coronary aneurysms. Occasionally, patients who develop myocardial ischemia may require coronary revascularization with either coronary bypass grafting, percutaneous coronary interventions or even cardiac transplantation. Additionally, the presence of Kawasaki disease may be a harbinger for early onset coronary artery disease in adults.

### **Resumen**

La enfermedad de Kawasaki es una vasculitis sistémica de la niñez, con predilección para afectar las arterias coronarias, y que constituye la principal causa de enfermedad cardíaca adquirida en la edad pediátrica en países desarrollados. Su prevalencia es

significativamente mayor en niños de ascendencia asiática, pero ocurre en otros grupos étnicos alrededor del mundo. Ocasionalmente, su diagnóstico se hace difícil en su etapa más temprana, suscitando un problema clínico serio, ya que la administración de la terapia indicada en las primeras horas de la enfermedad, es lo que de forma más significativa se ha asociado a reducción en el desarrollo de aneurismas en las arterias coronarias. El desarrollo de estas lesiones, particularmente los aneurismas múltiples o gigantes, puede llevar a complicaciones cardiovasculares serias tanto en la niñez como en la adultez, como: isquemia e infartos del miocardio, obstrucción o ruptura de los vasos coronarios u ocasionar la muerte de forma súbita. Como en el caso descrito en este informe, el tratamiento a largo plazo de pacientes con aneurismas coronarios incluye el uso de agentes antiplaquetarios y anticoagulantes orales y a veces la utilización de revascularización coronaria, quirúrgica o percutánea. El manejo eficaz de estos pacientes requiere además, seguimiento médico adecuado enfocado al control de los factores de riesgo tradicionales para enfermedad coronaria y la utilización de métodos diagnósticos efectivos para la detección y manejo de isquemia del miocardio.

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