Coronary Artery Aneurysms and Thrombosis in Kawasaki Disease

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As per Journal Policies, ethical approval was not required for this manuscript

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This article does not contain any studies conducted with animals or on living human subjects

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No identifiable personal data were presented in this manuscript

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Kawasaki disease (KD) is an acute vasculitis of unknown etiology occurring in infants and young children and affecting medium-sized muscular arteries. It is a systemic disease, with possibly morbid to mortal manifestations in the cardiovascular system, including lymphocytic myocarditis and acute vasculitis associated with thrombosis and/or aneurysm formation. In regards to aneurysm formation, coronary artery involvement occurs in up to 40% of patients and can range from transient, mild dilatation or ectasia to giant coronary artery aneurysm. Treatment with aspirin and intravenous immunoglobulin (IVIG) therapy greatly reduces the occurrence of coronary artery aneurysm. Patients with large or giant coronary artery aneurysms are especially at risk for cardiac events including coronary artery thrombosis or stenosis, myocardial infarction, arrhythmias, and death (1).

A 7-month-old male infant was brought to the hospital after being found by his foster parents to be inconsolable and crying. He was up-to-date on his immunizations and met all his developmental milestones. Significant birth history included intrauterine exposure to methamphetamine, with a positive methamphetamine drug screen at birth, and subsequent removal from his mother and placement with a foster family.

A month earlier, he presented to an emergency department with symptoms of diarrhea for one week, loss of appetite, fever, pink eye, and rash on his entire body. A pediatrician diagnosed him with gastroenteritis secondary to adenovirus, he was treated with intravenous fluids, and he was released three days later with instructions to continue with oral rehydration with Pedialyte.

He continued to have intermittent loss of appetite and diarrhea, change of personality from being a happy baby to one with low energy, and significant weight loss. Worried, his foster parents brought him to the emergency department.

At the emergency department, he became tachycardic, displayed decreased capillary refill, and had episodes of apnea necessitating bag-mask ventilation. A complete blood count showed the white blood cell count

was elevated, but without profound left-shift, and he had mild anemia. While in the pediatric intensive care unit, an emergency bedside echocardiogram was done that showed markedly dilated coronary arteries consistent with Kawasaki disease. Despite aggressive management, he had multiple episodes of respiratory arrest without loss of pulse and was pronounced dead.

Autopsy examination revealed a pale infant with pale organs and an enlarged heart with thrombosed giant coronary artery aneurysms involving the proximal portions of the right coronary and the entire left anterior descending arteries (**Image 1A**). Both kidneys had multiple wedge-shaped acute cortical infarcts. Histopathologically, there were thrombosed aneurysms of the coronary arteries along with panvasculitis of the coronary arterial wall (**Images 1B** and **1C**), lymphocytic epicarditis, lymphocytic myocarditis, and multifocal contraction band necrosis (**Image 1D**). An interlobular aneurysm with thrombus formation was identified with panarteritis was seen in one of the kidneys (**Image 1E**).

The cause of death was determined to be complications of Kawasaki disease and the manner of death was natural.

The clinical diagnosis of Kawasaki disease, or mucocutaneous lymph node syndrome, requires the presence of a fever lasting for five or more days, accompanied by four out of five principal clinical findings including bilateral conjunctival congestion, oral changes such as strawberry tongue and cracked and erythematous lips, acute non-purulent cervical lymphadenopathy, extremity changes such as erythema or palm and sole desquamation, and polymorphous rash. Incomplete (atypical) Kawasaki disease occurs in patients with fevers lasting five or more days and with less than four of the clinical findings. A clinical diagnosis of Kawasaki disease can be made in patients with the incomplete form when coronary artery disease is detected by coronary angiography or two-dimensional echocardiography (2). Histologic descriptions are largely based on the most severe cases, as they reflect findings at the time of autopsy (1).

Image 1A: Enlarged heart with giant coronary artery aneurysms of the right coronary and left anterior descending arteries.

Prompt and early diagnosis within ten days of illness is imperative, so treatment with aspirin and intravenous immunoglobulins can be initiated. In nearly 15 to 25% of untreated patients, coronary artery aneurysms develop. If treated properly, the incidence of coronary artery aneurysm decreases to approximately 5% and development of giant coronary aneurysms to 1% (2). Giant coronary artery aneurysms are defined as aneurysms that measure greater than 8 mm in diameter. This finding is strongly associated with poor patient

outcome as the large aneurysm size increases the risk of thrombosis, rupture, stenosis, myocardial infarction, and sudden death (3, 4).

Diagnosis of Kawasaki disease can be challenging as it mimics other common illnesses and drug reactions, and thus diagnosis is often delayed. Infants presenting with incomplete (atypical) Kawasaki disease are at a heightened risk for delayed diagnosis and the development of coronary artery aneurysms (5, 6). Risk fac-

Image 1B: Coronary artery with aneurysm, thrombus and panvasculitis (H&E, x20).

tors for development of coronary artery aneurysms, particularly giant coronary artery aneurysms, include young infants, males, persistent fevers, laboratory signs of inflammation, Asian ancestry, Hispanic children (intermediate risk), longer interval to diagnosis and treatment, and recurrent disease (7-10). Giant coronary artery aneurysm confers a high risk for thrombosis, as was seen in this patient (3, 4).

There is a progression to the histopathology findings in the coronary arteries in Kawasaki disease that mir-

rors patient risk and disease state. Coronary arteritis is first seen six to eight days after the onset of disease. Beginning at day ten, the arterial walls are infiltrated by lymphocytes and macrophages with subsequent panvasculitis and damage of the internal elastic lamina and medial smooth muscle cells. Around day 12, aneurysms start to form, if the damage is severe, and thrombosis may occur since blood pools in the aneurysms. Inflammatory infiltrates continue to be present until the 25th day of the disease, and then will gradually decrease and be almost completely gone

Image 1C: Higher magnification of thrombus with lymphocytic panvasculitis and surrounding epicarditis (H&E, x100).

by day 40. Scars from the inflammation will remain (11). Lymphocytic myocarditis is commonly found in Kawasaki disease and can be responsible for cardiac dysfunction (12).

Kawasaki disease is an infrequent entity seen in the medical examiner setting. Delay in clinical diagnosis can lead to coronary artery aneurysm and thrombosis and sudden death. Mortality/morbidity due to sequelae of persistent/remodeled cardiac damage can be seen in the adult population (13).

Image 1D: Myocardium with contraction band necrosis (H&E, x400).

Image 1E: Kidney with thrombus in arcuate artery and associated vasculitis (H&E, x20).

REFERENCES

- 1) Newburger JW, Takahashi M, Burns JC. Kawasaki disease. *J Am Coll Cardiol*. 2016 Apr 12; 67(14):1738-49. PMID: 27056781. <https://doi.org/10.1016/j.jacc.2015.12.073>.
- 2) Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation*. 2004 Oct 26; 110(17):2747-71. PMID: 15505111. <https://doi.org/10.1161/01.CIR.0000145143.19711.78>.
- 3) Patil S, Shirodkar S, Pinto RJ, Dalvi B. Giant coronary artery aneurysm with a thrombus secondary to Kawasaki disease. *Ann Pediatr Cardiol*. 2008 Jan; 1(1):59-61. PMID: 20300241. PMCID: PMC2840734. <https://doi.org/10.4103/0974-2069.41059>.
- 4) Kato H, Sugimura T, Akagi T, et al. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996 Sep 15; 94(6):1379-85. PMID: 8822996. <https://doi.org/10.1161/01.cir.94.6.1379>.
- 5) Chang FY, Hwang B, Chen SJ, et al. Characteristics of Kawasaki disease in infants younger than six months of age. *Pediatr Infect Dis J*. 2006 Mar; 25(3):241-4. PMID: 16511387. <https://doi.org/10.1097/01.inf.0000202067.50975.90>.

- 6) Liu HC, Lo CW, Hwang B, Lee PC. Clinical manifestations vary with different age spectrums in infants with Kawasaki disease. *Scientific World Journal*. 2012; 2012:210382. PMID: 22454602. PMCID: PMC3289979. <https://doi.org/10.1100/2012/210382>.
- 7) Minich LL, Sleeper LA, Atz AM, et al. Delayed diagnosis of Kawasaki disease: What are the risk factors? *Pediatrics*. 2007 Dec; 120(6):e1434-40. PMID: 18025079. <https://doi.org/10.1542/peds.2007-0815>.
- 8) Belay ED, Maddox RA, Holman RC, et al. Kawasaki syndrome and risk factors for coronary artery abnormalities: United States, 1994-2003. *Pediatr Infect Dis J*. 2006 Mar; 25(3):245-9. PMID: 16511388. <https://doi.org/10.1097/01.inf.0000202068.30956.16>.
- 9) Nakamura Y, Yashiro M, Uehara R, et al. Case-control study of giant coronary aneurysms due to Kawasaki disease. *Pediatr Int*. 2003 Aug; 45(4):410-3. PMID: 12911476. <https://doi.org/10.1046/j.1442-200x.2003.01744.x>.
- 10) McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. *Circulation*. 2007 Jul 10; 116(2):174-9. PMID: 17576863. <https://doi.org/10.1161/CIRCULATIONAHA.107.690875>.
- 11) Takahashi K, Oharaseki T, Yokouchi Y. Pathogenesis of Kawasaki disease. *Clin Exp Immunol*. 2011 May; 164 Suppl 1:20-2. PMID: 21447126. PMCID: PMC3095860. <https://doi.org/10.1111/j.1365-2249.2011.04361.x>.
- 12) Harada M, Yokouchi Y, Oharaseki T, et al. Histopathological characteristics of myocarditis in acute-phase Kawasaki disease. *Histopathology*. 2012 Dec; 61(6):1156-67. PMID: 23134515. <https://doi.org/10.1111/j.1365-2559.2012.04332.x>.
- 13) Daniels LB, Gordon JB, Burns JC. Kawasaki disease: late cardiovascular sequelae. *Curr Opin Cardiol*. 2012 Nov; 27(6):572-7. PMID: 23075819. <https://doi.org/10.1097/HCO.0b013e3283588f06>.