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# Review of Kawasaki Disease

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## **A review of Kawasaki disease**

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## Abstract

**Background:** Kawasaki disease is one of the leading causes of acquired heart disease in children. It is an acute self-limited vasculitis that predominantly affects infants and children younger than 5 years of age. These patients present with nonspecific symptoms, such as fever and lymphadenopathy, making the diagnosis challenging. This disease can have serious and potentially fatal outcomes, and prompt recognition of this disease is vital to the patient's outcome. We present a complete review of the disease, including the epidemiology, pathophysiology, diagnosis and management of acute Kawasaki disease, the natural history of this disease, and follow up of these patients as they transition into the adult cardiology practice.

**Methods:** Our systematic review information was collected from articles retrieved from PubMed library. Keywords that were used included; Kawasaki disease, coronary artery disease, coronary artery aneurysm, pediatric coronary artery disease, epidemiology of Kawasaki disease and treatment of Kawasaki disease. We included only relevant to the topic articles. No exclusion criteria were applied.

**Conclusions:** Kawasaki disease incidence tends to be increasing over the last decade in the United States. Seasonality of the disease has been described in Japan. It is a mysterious disease with unknown etiology, however, multiple hypotheses have been proposed and tested to explain the pathophysiology. As this disease has an associated high morbidity and mortality, prompt recognition and management are important to the patient's overall prognosis and survival.

## Keywords

Kawasaki disease, coronary artery aneurysms, coronary artery disease

## Introduction

Kawasaki disease (KD), previously known as mucocutaneous lymph node syndrome, is an acute self-limited vasculitis that predominantly affects infants and children younger than 5 years of age. The disease was first described in Japan by Tomisaku Kawasaki in 1967 and is known to occur in both Americas, Europe, and Asia; Japan has recorded the highest incidence and prevalence of the disease across the globe.<sup>1,2,3</sup> Patients present with nonspecific symptoms, such as fever and lymphadenopathy, making the diagnosis challenging.<sup>3</sup> Kawasaki disease can have serious and potentially fatal outcomes, and prompt recognition of this disease is vital to the patient's outcome.

## Methods

Our systematic review information was collected from articles retrieved from PubMed library. Keywords that were used included: Kawasaki disease, coronary artery disease, coronary artery aneurysm, pediatric coronary artery disease, epidemiology of Kawasaki disease and treatment of Kawasaki disease. We included only relevant to the topic articles. No exclusion criteria were applied. Twenty-eight articles were selected as a source of information.

## Epidemiology

The prevalence of KD is reportedly the highest in Japan and in those with Japanese descent.<sup>4</sup> In 2012, data from Japan revealed that the annual incidence was 264.8 cases per 100,000 children aged 0-4 years per year.<sup>5</sup> Reported data from US has been based on hospital discharge data; it appears that in 2000, 4248 hospitalizations in patients with KD were noted and there has not been a significant increase in the last decade.<sup>6</sup> In regard to gender, data from the United States reports an incidence of boys: girls at 1.5:1, suggesting that this disease is more common in males.<sup>5</sup> Interestingly, there are also seems to be an association with seasonality. Japan and Korea have both reported peaks in January and July, with a nadir in October.<sup>7-9</sup> In contrast, KD occurs more commonly during the winter and early spring months in the United States.<sup>10</sup> The fatality rate from KD in Japan has been reported as high as 0.08% and all deaths from KD are a result of cardiac sequelae.<sup>3</sup>

## Pathophysiology

The etiology of this mysterious disease is unknown and there have been multiple attempts to explain this disease by an infection and toxins, however, trials have failed to show an association. As young infants rarely have been reported to have this disease, there is a theory that there is some protection from maternal antibodies.<sup>3</sup>

On a microscopic level, in acute KD it has been shown that both the innate and adaptive immune systems are involved. Neutrophils are among the first responders to invade the arterial wall and are followed by CD8+ T cells, dendritic cells, and monocyte/macrophages.<sup>11,12</sup> Increased transcript abundance for IL-1 related genes by microarray and quantitative real-time polymerase chain reaction, and increased levels of IL-1 pathway proteins in plasma support the activation of the interleukin (IL)-1 pathway in Kawasaki disease.<sup>13</sup>

Also in KD, as in giant cell arteritis,<sup>14</sup> two dominant cytokine clusters are recognized: the IL-6/T helper (Th)-17 axis and the IL-12/interferon gamma axis. IL-6, in combination with transforming growth factor beta (TGFβ), polarizes naïve T cells toward a Th-17 phenotype, resulting in these cells invading the vessel wall and elaborating a proinflammatory cytokine profile.<sup>15,16</sup>

## Diagnosis

With the unknown and unidentified etiology of Kawasaki disease, the diagnosis remains based on careful clinical evaluation of patients with suspected KD.<sup>17</sup> The nonspecific symptoms and signs of KD are shared with multiple other diseases and conditions, thus, one should be very thorough and systematic to rule out a broad differential diagnosis (Table 1).<sup>18</sup> The 2004 American Heart Association (AHA) guidelines and the fifth edition of the Japan Diagnostic Guidelines (JDG) both list six principal clinical features for KD diagnosis.<sup>3,17</sup> While the AHA guidelines considers having a prolonged fever (more than five days) an essential element for the diagnosis of KD, the JDG gives the prolonged fever equal weight to other clinical features.<sup>3,17</sup> Along with prolonged fever, patients who meet complete (typical) AHA KD diagnosis criteria should also have four of the following principal clinical features: 1) bilateral conjunctival injection, 2) changes of the mucous membranes (chapped lips, strawberry tongue, or injected pharynx, 3) polymorphous skin rash, 4) changes in the extremities (swelling of hands and feet,

erythema, or periungual desquamation), 5) cervical lymphadenopathy (usually unilateral, and it is the least common finding).<sup>3</sup>

Viral disease	Measles, Epstein-Barr Virus (Mononucleosis), Influenza, Adenovirus, and Enterovirus
Bacterial Infections	Scarlet Fever, Staphylococcal Scalded Skin Syndrome, Mycoplasma infections, Rocky Mountain Spotted Fever, Leptospirosis, and Bacterial Cervical Lymphadenitis (abscesses)
Immunological, or autoimmune	Drug reactions, Vaccine reactions, Juvenile rheumatoid arthritis, Mercury hypersensitivity reaction, and insect bites

Not all patients with suspected KD develop five principal clinical features. There is a portion of KD patients that develop four or less of the principal symptoms and signs.<sup>4</sup> These subsets of patients have been described under the term of atypical (or incomplete) KD.<sup>3</sup> Atypical KD has been described mostly in ages less than 6 months and older than 10 years.<sup>19</sup> These patients have a higher incidence rate of coronary artery lesions, the major complication of KD.<sup>19</sup> As atypical KD cases do not fulfill the criteria for complete KD diagnosis, the evaluating clinician should look for other supportive clinical and laboratory supplementary findings of KD. The supplementary findings are detailed by systems in Table 2.<sup>3,17</sup> With the suspicion of KD (prolonged fever) and incomplete fulfillment of clinical criteria (presence of 2 or 3 other principal clinical features), patients should undergo continuous clinical reassessment to look for further development of the missing principal features. Simultaneously, laboratory evaluation should take place to look for supplementary laboratory evidence (Table 2). If the patient meets incomplete criteria for KD, echocardiographic evaluation is warranted.<sup>3</sup>

Table 2: Other significant symptoms and findings for patients with suspected KD. Findings are listed by systems.	
Cardiovascular	Findings consistent with heart failure, myocardial infarction, or arrhythmias (heart murmur, gallop, prolonged PR, QT, ST changes, EKG findings consistent with arrhythmias, radiologic or echocardiographic findings of congestive heart failure); aneurysms of coronary arteries and non-coronary medium sized arteries
Gastrointestinal	Diarrhea, vomiting, abdominal pain, hydrops of gall bladder, ileus, hypoalbuminemia, transaminitis, and jaundice
Hematopoietic	Leukocytosis with leftward shift, thrombocytosis, and anemia
Renal	Proteinuria, and sterile pyuria
Skin	Reaction to Bacille Calmette-Guèrin inoculation with redness and induration; pustules
Neurological	Irritability, pleocytosis of cerebrospinal fluid, seizures, peripheral facial palsy, and paralysis of extremities
Musculoskeletal and inflammatory	Arthralgia, joint swelling; elevated erythrocyte sedimentation rate (ESR), elevated C-reactive protein(CRP)
Respiratory	Rhinorrhea, cough
Laboratory findings	Leukocytosis with leftward shift Elevated ESR Elevated CRP Anemia Abnormal plasma lipids Hypoalbuminemia Hyponatremia Thrombocytosis after week 1 Sterile pyuria Elevated serum transaminases Elevated serum gamma glutamyl transpeptidase Pleocytosis of cerebrospinal fluid Leukocytosis in synovial fluid

### Management of Acute KD

The main rationale behind administering the acute treatment for KD cases is to prevent coronary artery lesions and decrease its burdens.<sup>3</sup> Optimally, and to have the best response, acute treatment should be instituted in the first ten days of illness.<sup>3</sup> The most effective regimen that has been described consists of high dosage (2g/kg) of intravenous immunoglobulin (IVIG) infusion.<sup>3</sup> Along with IVIG infusion, a high dosage of aspirin (80 to 100 mg/kg/day) should be administered to achieve anti-inflammatory and antiplatelet effect.<sup>3</sup> IVIG should be infused slowly over eight to twelve hours. Infusion may be repeated if fever persists 36-48 hours after the first infusion.<sup>3</sup> High dosage aspirin is recommended during the period that the patient is symptomatic (usually the first 48 hours).<sup>3,17</sup> Antiplatelet aspirin dosage (5 mg/kg/day) is indicated until long-term follow up is completed.<sup>3,17</sup> Other regimens of acute treatment for KD,



most commonly conjunctive use of steroids, have been described in cases of resistant KD cases.<sup>20,21</sup>

The ultimate management of patients with KD also requires an initial echocardiographic evaluation of their coronary arteries along with complete echocardiographic study.<sup>3</sup> This baseline echocardiographic coronary evaluation helps stratify the coronary risk for patients with KD, and it determines the antithrombotic treatment and follow-up schedule they should follow.<sup>7</sup> Patients with no coronary artery lesions (Z Scores < 2) should be on low dosage aspirin (antiplatelet therapy) for four to six weeks, with repeated echocardiographic evaluations in two weeks and six to eight weeks after the onset of illness.<sup>3</sup> Patients with higher coronary risks with dilated coronary artery diameters (Z scores > 2.5) will undergo a lifelong follow up for surveillance of worsening aneurysms and tailoring of antithrombotic treatment based on their coronary risk.<sup>22,23</sup>

### **Natural History and Cardiac Findings**

Cardiac findings that have been reported in the literature include coronary aneurysms, myocarditis, mitral regurgitation from papillary muscle dysfunction, myocardial infarction, or valvulitis. These abnormalities can be identified by echocardiography, magnetic resonance imaging (MRI)/magnetic resonance angiogram (MRA), and/or cardiac angiography.<sup>3</sup>

With a specific focus on coronary artery aneurysms, it is noted that the morphology of coronary arteries changes dynamically with time in KD. Aneurysms may increase in size in the first two months of illness; resolution generally occurs in one to two years in 50-67% of patients after disease onset.<sup>24,25</sup> The resolution of the aneurysm depends on multiple factors such as the age of onset of disease, initial morphology, location and size of aneurysm. For example, the smaller the size of aneurysm, the greater the likelihood of resolution. The worst consequences appear to occur in giant aneurysms (maximum diameter >8mm).<sup>26</sup> In giant aneurysms, there can be stenotic lesions on either side of the aneurysmal sac due to marked proliferation of the myointima, which can result in high morbidity and mortality.<sup>25</sup> Interestingly, the coronary artery aneurysms that undergo resolution have an abnormal histopathology; specifically, they have a decreased vascular response to isosorbide dinitrate, indicating endothelial dysfunction.<sup>27</sup>

Therapeutic regimens to prevent thrombosis of coronary arteries in these patients include antiplatelet therapy with aspirin, +/- clopidogrel or dipyridamole, anticoagulation with warfarin, or a combination of antiplatelet and anticoagulant therapy based on risk stratification (see below). It should be noted, however, that these patients who develop acute thrombosis should not be treated as if this was due to plaque rupture; therefore, thrombolytics have been suggested and therapy with aspirin, heparin, and glycoprotein IIb/IIIa inhibitors should be utilized. Catheter intervention with balloon angioplasty, rotational ablation, and stent placement can be utilized; however, if this is not successful and the patient has severe left ventricular dysfunction or vessels with multiple, ostial, or long-segment lesions, then coronary artery bypass surgery is recommended.<sup>3</sup>

Patients with KD tend to have higher adverse cardiac risk profiles, with higher blood pressures and derangements in lipid profiles.<sup>28</sup> The population of children with KD reaching adulthood is growing. Hence, risk stratification and follow up of these patients are vital for long-term

management. Listed below is a consensus by experts in regard to classifying these patients and management.<sup>3</sup>

- Risk Level I: echocardiography does not show any coronary artery changes at any stage of the illness
  - Pharmacological therapy: none beyond 1<sup>st</sup> 6-8 weeks
  - Physical activity: no restrictions beyond 1<sup>st</sup> 6-8 weeks
  - Follow up and Diagnostic Testing: cardiovascular risk assessment, counseling at 5-year intervals
  - Invasive testing: not recommended
- Risk Level II: echocardiography shows transient coronary artery ectasia or dilatation that is known to disappear within the first 6-8 weeks
  - Pharmacological therapy: none beyond 1<sup>st</sup> 6-8 weeks
  - Physical activity: no restrictions beyond 1<sup>st</sup> 6-8 weeks
  - Follow up and Diagnostic Testing: cardiovascular risk assessment, counseling at 3-5 year intervals
  - Invasive testing: not recommended
- Risk Level III: echocardiography or angiography shows isolated (solitary) small to medium (3-6 mm or Z score between 3 and 7) coronary artery aneurysm in  $\geq 1$  coronary arteries
  - Pharmacological therapy: low dose aspirin (3-5 mg/kg aspirin/d), at least until aneurysm regression is documented
  - Physical activity:
    - <11 years of age: no restrictions beyond 1<sup>st</sup> 6-8 weeks
    - 11-20 years of age: physical activity guided by stress test, evaluation of myocardial perfusion scan; contact or high-impact sports discouraged for patients taking antiplatelet agents
  - Follow up and Diagnostic Testing: annual cardiology follow up with echocardiogram and EKG, combined with cardiovascular risk assessment counseling; biennial stress test/evaluation of myocardial perfusion scan
  - Invasive testing: angiography if noninvasive test suggests ischemia
- Risk Level IV:  $\geq 1$  large coronary artery aneurysm ( $\geq 6$  mm) and coronary artery that contains multiple (segmented) or complex aneurysms without obstruction
  - Pharmacological therapy: long-term antiplatelet therapy + warfarin with INR goal 2-2.5 OR low molecular weight heparin (target antiXa level of 0.5-1.0) should be combined in giant aneurysms
  - Physical activity: avoid contact or high-impact sports due to higher risk of bleeding; other restrictions are guided by stress test/evaluation of myocardial perfusion scan outcome
  - Follow up and Diagnostic Testing: biannual follow up with echocardiogram and EKG; annual stress test/evaluation of myocardial perfusion scan
  - Invasive testing: first angiography at 6-12 months or sooner if clinically indicated; repeated if noninvasive testing, clinical/laboratory findings suggest ischemia

- Risk Level V: angiography confirms the presence of coronary artery obstruction
  - Pharmacological therapy: long-term low-dose aspirin; if presence of giant aneurysm, add warfarin or low molecular weight heparin; consider beta blockers to reduce myocardial oxygen consumption
  - Physical activity: avoid contact or high-impact sports due to higher risk of bleeding; other restrictions are guided by stress test/evaluation of myocardial perfusion scan outcome
  - Follow Up and Diagnostic Testing: biannual follow up with echocardiogram and EKG; annual stress test/evaluation of myocardial perfusion scan
  - Invasive testing: angiography recommended to address therapeutic options

## Case

We present a case of a 32 year old male with a history of Kawasaki disease with known coronary artery aneurysms, hypertension and hyperlipidemia, taking rivaroxaban, managed at an outside facility who was referred after a positive exercise stress test ordered for exertional chest pain and dyspnea. He was found to have marked ST segment depressions, mainly in the inferior leads, when walking on the treadmill. Subsequent left heart catheterization revealed large aneurysms in the left anterior descending and right coronary artery with critical stenosis (Figures A & B). The patient was referred for cardiac bypass surgery for further management.

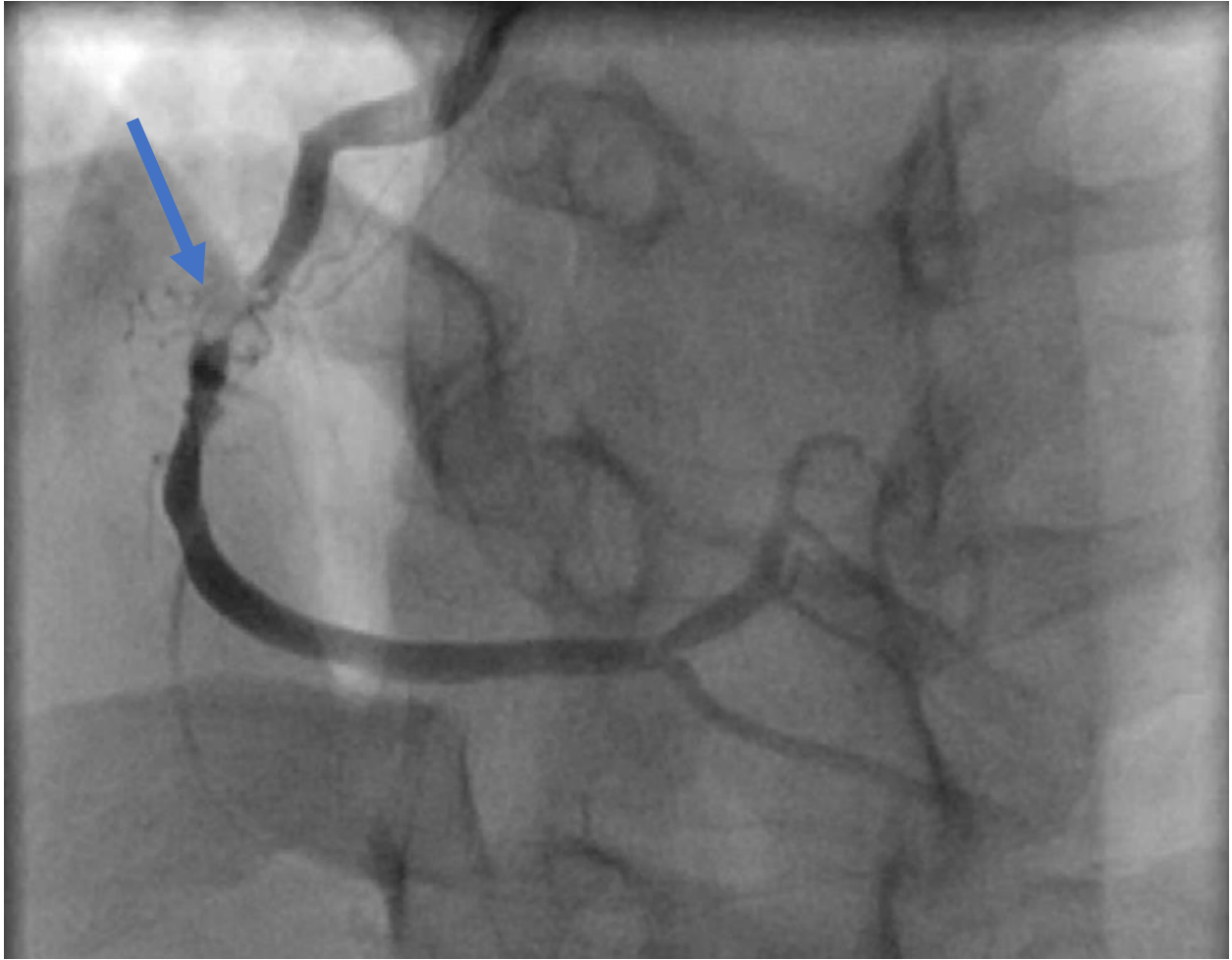


Figure A: Mid RCA with thrombosed aneurysm

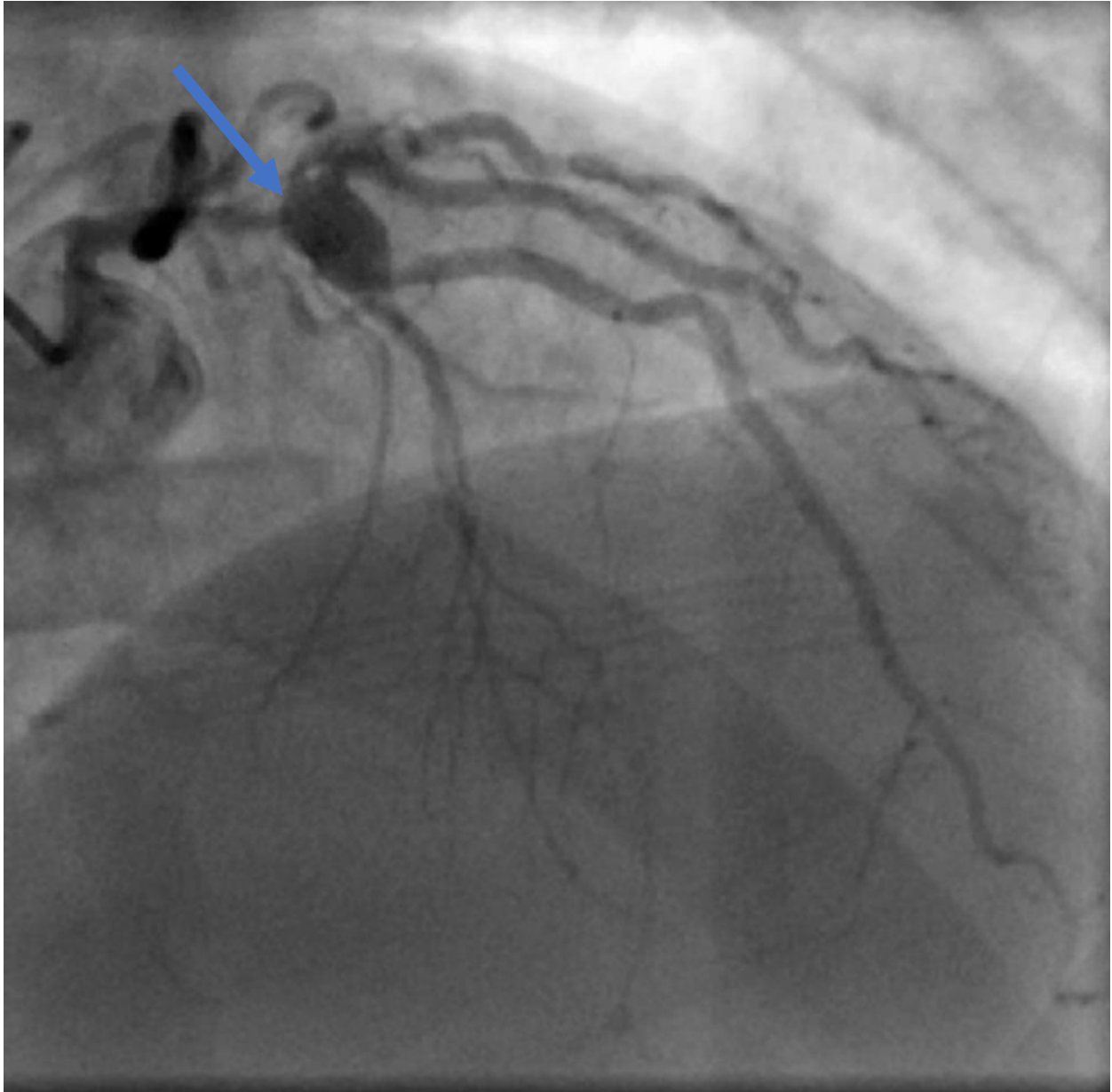


Figure B: Aneurysm of the proximal left anterior descending artery

## Summary

KD is one of the leading causes of acquired cardiac disease in children, noted to be higher in incidence in Japan and the United States. As with our patient, coronary aneurysms have been known to be a common sequela of this disease. Therefore, prompt recognition and treatment during the acute phase of KD is important. For those patients with residual coronary disease, prevention and management of myocardial ischemia and dysfunction are paramount.

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