

## Coronary Artery Sequel of Kawasaki Disease in Adulthood, a Concern for Internists and Cardiologists

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### ABSTRAK

*Dewasa muda yang mengalami kejadian jantung akut (acute cardiac event) seperti sindrom koroner akut, aritmia yang terkait dengan iskemia dan kematian mendadak, seringkali tidak diketahui penyebabnya dan juga tidak mempunyai faktor risiko yang bermakna. Vaskulitis koroner akibat penyakit Kawasaki turut berperan sebagai faktor risiko pada populasi dewasa muda dan menimbulkan kejadian koroner akut. Penyakit Kawasaki terutama menyerang di masa kanak-kanak, menyebabkan vaskulitis arteri koroner dan hal ini menjadi perhatian utama karena menimbulkan aneurisma dan stenosis di kemudian hari. Penyakit Kawasaki bersifat swa-sirna atau dapat sembuh dengan sendirinya, sehingga penderita penyakit ini di masa kanak-kanak dapat bertahan hingga masa dewasa. Bertambah cepatnya proses aterosklerosis koroner yang terjadi pada lesi yang terkait dengan penyakit Kawasaki pada dewasa muda serta sindrom koroner akut dan kematian mendadak yang menyertai pada populasi ini merupakan dampak buruk dan gejala sisa yang sangat memprihatinkan dari penyakit ini. Diharapkan, para ahli penyakit dalam dan kardiologi dewasa dapat mengenali gejala sisa ini dan menyediakan layanan yang lebih baik bagi para pasien.*

**Kata kunci:** *penyakit Kawasaki, aneurisma koroner, aterosklerosis.*

### ABSTRACT

*Young adults suffered from acute cardiac event, such as acute coronary syndrome, ischemic-associated arrhythmia and sudden death, are frequently encountered without known etiology and significant risk factors. Coronary vasculitis due to Kawasaki disease contributes to be a risk factor in young adult population to develop acute coronary event. Afflicted predominantly during childhood, Kawasaki disease gives rise to vasculitis of coronary artery which becomes major concern since it leads to coronary aneurysm and stenosis. Self-limited nature of Kawasaki disease make those suffered in childhood survive into adult life. Accelerated coronary atherosclerosis in the Kawasaki disease-related lesion occurring in young adult and subsequent acute coronary syndrome and sudden death in this population are devastating impacts of the sequel of Kawasaki disease. It is expected that internists and adult cardiologists become familiar with this sequel and provide better care for the patients.*

**Key words:** *Kawasaki disease, coronary aneurysm, atherosclerosis.*

## INTRODUCTION

Doctor Tomisaku Kawasaki, a Japanese pediatrician, first reported the new syndrome occurring in 50 Japanese children between 1961 and 1967.<sup>1</sup> This syndrome is known as Kawasaki disease or Kawasaki syndrome.<sup>1</sup> Kawasaki disease currently becomes the most common acquired heart disease in children among developed countries, especially in Japan, where its incidence is ten times higher than it is in Western countries.<sup>2</sup> There is a predilection towards Asian population, although the syndrome occurs in all other races as well.<sup>3,4</sup>

Initially, this disease is thought to be a pediatric problem, because its self-limited nature. After populational study involving long term follow-up of children affected with Kawasaki disease, the natural history of this disease becomes apparent that it will cause sequel in adult life.<sup>2,3</sup> The natural history of Kawasaki disease before the era of intravenous immunoglobulin is as follows: 1) approximately 20%-25% of children developed coronary artery aneurysms as a sequel of coronary artery vasculitis, (2) patients who developed coronary artery aneurysms during acute phase, 20% will progress to coronary artery stenosis and (3) myocardial ischemia and infarction, even sudden cardiac death, is potentially occur in relatively young age, which need treatment such as percutaneous coronary intervention, coronary artery bypass grafting, and even cardiac transplantation.<sup>3</sup>

As children with acute phase of Kawasaki disease mostly survived, the sequel of coronary lesion will develop in adult life. Accelerated coronary atherosclerosis occurring in relatively young age is contributed mainly by Kawasaki disease sequel, which leads to acute coronary syndrome and sudden death in this population. While pediatricians care children with acute phase of Kawasaki disease, internists and adult cardiologists may care these patients in adult life. Sometimes their childhood medical history of Kawasaki disease was not documented, even undiagnosed. Thus, understanding the sequel of this disease in adult life is of paramount important for internists and adult cardiologists. This review provides an information regarding sequel of Kawasaki disease which affect coronary artery in adult life.

## KAWASAKI DISEASE IN CHILDHOOD

Kawasaki disease is an acute systemic inflammatory disease involving multiple organs and tissues, with coronary artery vasculitis is the most clinically significant feature.<sup>4</sup> This disease is a self-limited syndrome.<sup>3-5</sup> Kawasaki disease developed over first ten days of febrile illness and than steadily disappear in most children, even without specific therapy.<sup>6</sup>

Children with age between 6 months and 5 years were predominate age groups susceptible for Kawasaki disease.<sup>3,5,6</sup>

Fever for at least five days' duration, with at least four of the following five clinical features: 1). polymorphous exanthema (but not petechial, bullous, or vesicular lesions); 2). bilateral non-exudative conjunctival injection; 3). changes in lips and oral cavity (but not discrete oral lesions or exudates); 4). changes in the extremities, including erythema or indurative oedema, and later (in the second week of illness) membranous desquamation starting around the nail bed; 5). cervical lymphadenopathy, often unilateral and large.

Children who meet the above criteria are diagnosed with complete Kawasaki disease. Since there is no specific diagnostic tool for Kawasaki disease, clinical diagnostic criteria must be examined carefully to avoid misdiagnosis.

Incomplete or atypical form of Kawasaki disease is diagnosed if children in suspicion do not meet the above criteria. This term is used for children with fever at least five days and at least two of the above criteria without other explainable illness and laboratory examination revealed systemic inflammation (high level of C reactive protein or erythrocyte sedimentation rate).<sup>6</sup> Incomplete (atypical) Kawasaki disease often suffers from coronary artery abnormality seen on echocardiography.<sup>5,6</sup>

Along with clinical features which appear sequentially, laboratory examination reveals following features during 7-10 days of disease:<sup>6</sup> 1). rutin haematology: elevated leukocyte count with neutrophilia (at least 50% of cases), progressive anaemia (usually normocytic and normochromic), increased platelet count (peak in the second or third week of illness). 2). urinalysis: urinary sediment may contain increased numbers of leukocytes without bacteruria; 3). acute phase

proteins: elevated C reactive protein (>35mg/l in 80% of cases), erythrocyte sedimentation rate (>60 mm/h in 60% of cases); 4). blood chemistry: low serum sodium, low serum protein and albumin, elevated liver enzymes (specifically alanine aminotransferase), and abnormal blood lipid profile; 5). cerebrospinal fluid: pleocytosis, usually lymphocytic with normal protein and glucose.

Systemic vasculitis frequently developed in Kawasaki disease, with coronary artery can be severely affected. Thus cardiac examination must be completed as part of examination. Electrocardiography and echocardiography examinations are mandatory.<sup>6</sup>

**Electrocardiography.** Sinus tachycardia with decreased QRS voltages, flattened T waves, and prolonged QTc intervals. These features are almost always reversible. Heart block may occur. In untreated large coronary artery aneurysms, electrocardiography may show signs of myocardial infarction as a result of coronary thrombosis.

**Echocardiography.** Decreased left ventricular function, mitral regurgitation, and pericardial effusion may be seen. Coronary artery dilatation could be observed starting an average of 9-10 days after onset of fever and occurs in 30-50% of cases.

Cardiac involvement constitute of myocarditis, pericarditis with pericardial effusion and valvulitis. Pericarditis and small pericardial effusions will resolve spontaneously without sequel in almost all of the patients.<sup>7</sup> Valvulitis in acute phase of Kawasaki disease develops in 2% of patients, most commonly in the mitral valve which will become scarring and incompetence.<sup>8</sup> Early myocardial involvement always resolves completely and does not necessarily associate with coronary artery involvement. Long-term myocardial contractility and function measured by echocardiography is normal.<sup>9</sup>

#### KAWASAKI DISEASE IN ADULTHOOD

Kawasaki disease is rarely seen in infant aged less than 6 months and in adults, which supports the existence of an infectious agent for which maternal immunity is protective during infant and protective immunity development during adult life.<sup>10</sup> Although very rare, several case reports

showed that acute phase of Kawasaki disease occurred in adult patients.<sup>11</sup> Similar to that in children, no specific diagnostic tool is available for acute Kawasaki disease in adulthood, thus clinician relies on meticulous findings of clinical diagnostic criteria.

Kawasaki disease in adulthood mimics several diseases with fever, cutaneous rash, mucosal involvement and cervical lymphadenopathy, such as scarlet fever, Still's disease, systemic lupus erythematosus, meningococemia, staphylococcal scalded-skin syndrome, Stevens-Johnson syndrome, and several viral rash fever.<sup>11</sup>

The clinical diagnostic criteria for Kawasaki disease in adulthood are similar to those of in the children. The presence of coronary artery aneurysm and sequel after acute Kawasaki disease in adulthood are unknown, since long term follow-up data unavailable.

#### TREATMENT OF KAWASAKI DISEASE

##### Intravenous Immunoglobulin

Randomized controlled trials have shown that a single infusion of 2 g/kg of intravenous immunoglobulin given 5-10 days after the onset of fever eliminates fever in 85-90% of children within 36 hours and significantly reduces the risk of coronary artery aneurysms.<sup>12</sup> Reduction of coronary artery aneurysm was achieved until 3.8% after the use of high-dose immunoglobulin therapy.<sup>13</sup>

##### Aspirin

Aspirin has been used in the treatment of Kawasaki disease due to its antiinflammatory effect at high doses and antiplatelet effect at low dose, however it does not decrease the incidence of coronary artery abnormalities.<sup>12</sup> During the acute phase of disease, aspirin is given at a dose 30 to 50 mg/kg divided into three doses afterward followed by 3 to 5 mg/kg once daily after recovery.<sup>13</sup> This combination has an additive antiinflammatory effect.<sup>12</sup> For children in whom aneurysms of the coronary arteries have been diagnosed, aspirin in an antiplatelet dose is continued on a daily basis as long as aneurysms persist and echocardiography examination is needed to evaluate the aneurysms.<sup>5,9</sup> The goal of this therapy is to prevent thrombosis and the myointimal proliferation that leads to coronary stenosis.<sup>14</sup>

### Corticosteroids

Before the era of intravenous immunoglobulin, a high incidence of coronary artery aneurysms was encountered in children with Kawasaki disease treated with corticosteroids as primary therapy. Randomized, controlled studies showed conflicting results of the use of corticosteroids for the primary treatment of Kawasaki disease.<sup>13</sup> Pulse corticosteroid did not add beneficial effect beyond standard therapy, i.e. intravenous immunoglobulin and aspirin<sup>15</sup>, however, methylprednisolon 30 mg/kg daily for 3 days is recommended if there is no response to the second cycle of intravenous immunoglobulin infusion.<sup>6</sup> In contrast to other systemic vasculitis, which usually respond to corticosteroids, Kawasaki disease vasculitis did not response well with corticosteroid.<sup>15</sup>

### CORONARY ANEURYSMS IN KAWASAKI DISEASE

The incidence of coronary aneurysm as a sequel of Kawasaki disease was 16.7% in year of 1983, at the time before intravenous immunoglobulin given as standard treatment, and was rapidly decreased to 3.8% in 2007 as the use of high-dose immunoglobulin therapy emerging.<sup>13</sup>

Mild diffuse dilatation of coronary arteries arises in 30-50% of acute Kawasaki disease children and begins approximately ten days from onset of febrile illness.<sup>12,16</sup> In the majority of cases, this mild dilatation is transitory and will regress within six to eight weeks of febrile onset<sup>9</sup>, the term called transient coronary dilatation.<sup>13</sup> Persistent coronary aneurysms in the recovery phase or afterward are considered sequel of Kawasaki disease.<sup>12,13</sup> Echocardiography examination during this time is an important tool to assess the coronary lesion and follow-up until recovery phase, around 30 day, is necessary for those with coronary lesion.<sup>13</sup>

Coronary artery vasculitis occurs during acute Kawasaki disease which features as endothelial cell swelling and subendothelial edema as well as mononuclear cells infiltration in coronary wall.<sup>17</sup> Internal elastic lamina is subsequently disrupted and myointimal proliferation within discrete area occurs.<sup>17</sup> Medial layer release matrix metalloprotease and vascular smooth muscle cell become necrotic and replace by fibrosis and calcification.<sup>18</sup> Imbalance between matrix metalloprotease and its tissue inhibitor may cause excessive fibrosis and aneurysms.<sup>19</sup>

Coronary aneurysms in Kawasaki disease can be divided based on its diameter:<sup>13</sup> (1) small aneurysms (internal diameter  $\leq 4$  mm), (2) medium aneurysms (internal diameter 4–8 mm) and (3) giant aneurysms (internal diameter  $> 8$  mm). Small aneurysms tend to undergo resolution and rarely progress to stenotic or thrombotic lesions.<sup>19</sup> Meanwhile, medium and giant aneurysms associated with thrombus occlusion on aneurysm site and even rupture of aneurysms, although wide range of remodeling processes occurs.<sup>13,20</sup>

In the late acute phase and early recovery phase of Kawasaki disease, coronary artery lesions undergo dynamic alteration and wide range of remodeling.<sup>2,13,20</sup> The prognosis of coronary artery aneurysms from Kawasaki disease is as follows: (1) Regression: regression of coronary artery aneurysms has been reported to occur in 50% to 67% of vessels with coronary aneurysms. This regression usually occurs within 1 to 2 years after onset. Typical aneurysms which tend to regress are small or medium aneurysms, fusiform aneurysm and distal coronary segment aneurysms.<sup>21</sup> Despite completely regress, such patients still need follow-up because coronary artery stenosis, coronary diastolic dysfunction and intimal hyperplasia may develop which lead to juvenile arteriosclerosis and myocardial ischemia.<sup>13</sup> (2) Occlusion: coronary artery occlusion develops early in less than 1% of cases, typically in giant aneurysms.<sup>20</sup> Total coronary occlusion can develop acute myocardial infarction which greatly contributes to mortality of Kawasaki disease in children. Occlusion of aneurysms can occur because of flow stagnation and the sudden reduction of shear stress in the aneurysm.<sup>22</sup> Occlusion happen in early phase can be caused by jelly-like extracellular matrix which formed plug in the vasculitis site or thrombus plug in aneurysms.<sup>23</sup> Intimal fibroblastic proliferation with superimposed thrombosis has also been observed.<sup>24</sup> (3) Occlusion with recanalization: Recanalization of coronary occlusion is typical of Kawasaki disease and give rise to neovascularization and collateral flow which rescue myocardia from infarcted.<sup>22</sup> About 15% of Kawasaki disease develops this recanalization or segmental stenosis which frequently (about 90%) occurs in right coronary artery.<sup>13</sup> (4) Localized stenosis: localized stenosis develops in about 10% in acute Kawasaki

disease.<sup>20</sup> Most of the localized stenosis occurs in the inlet and/or outlet of aneurysms, the site of high shear stress.<sup>22</sup> Shear stress promotes endothelial cell injury which induces intimal thickening and muscular proliferation lead to stenosis. During the period of up to 10 to 21 years after onset, localized stenosis of more than 75% vessel diameter develop in 4.7 to 12% of patients with coronary artery lesions and mainly occurs in the proximal segment of left anterior descending artery.<sup>13</sup>

In the late phase of disease, several years after acute phase subsided, coronary aneurysms will undergo regression, rupture, extension, calcification, occlusion, occlusion with recanalization or collateral vessels and localized stenosis.<sup>20</sup> Active remodeling of coronary artery lesions of Kawasaki disease are still taking place many years later, characterized by coronary artery intimal proliferation and various degrees of angiogenesis which were evident in autopsy pathology.<sup>23</sup> Regression of coronary artery aneurysms may be because of true healing or masquerading by intimal proliferation and thrombus organization, or arterial wall contraction due to scar formation which narrow coronary lumen.<sup>3</sup> Intravascular ultrasound study in the regressed coronary aneurysms shows marked symmetrical or asymmetrical myointimal thickening<sup>25</sup> and plaque area with various degrees of fibrous, fibrofatty changes, superficial dense calcium, and necrotic core components.<sup>26</sup>

Fibrous scar formation or calcification possibly develops in aneurysms years later.<sup>23</sup> Arterial wall calcification in the site of aneurysms or former aneurysms are pathognomonic sign of Kawasaki disease in later life.<sup>18</sup> In a report of Japanese young adults 20 years later after acute phase of Kawasaki disease, 94% of those with aneurysms at least 6 mm in internal diameter during the sub acute phase of the illness had calcification observed by electron beam computed tomography.<sup>27</sup> Calcification of Kawasaki disease differs from that of atherosclerotic calcification which tends to be localized in the pre-existing aneurysms site not diffuse calcification. Calcification in Kawasaki disease reflected the degree of acute vasculitis and subsequent intimal proliferation which localized in proximal coronary segment and rarely involve the small branches and peripheral

coronary arteries.<sup>28</sup> Localized proximal coronary calcification can be detected with cardiac X-ray and may help identify patients with Kawasaki disease.<sup>28</sup>

Coronary artery lesions characteristic of Kawasaki disease observed in adult life include giant aneurysms, coronary artery calcification, segmental stenosis with recanalization after thrombotic occlusion and aneurysms involving the left coronary artery bifurcation.<sup>28</sup> Angiography finding shows that coronary artery lesions of Kawasaki disease usually involve the proximal segments of the major branches, left anterior descending and right coronary arteries, and tend to be localized.<sup>29</sup> This nature consequently contributes to high possibility to develop acute coronary syndrome once the lesions become significant stenotic or thrombus occlusion.

Besides coronary artery aneurysms and stenosis, coronary artery of Kawasaki disease shows various degree of coronary artery dysfunction. Dilatation capacity, endothelial dependent or endothelial independent, and coronary-myocardial blood flow reserve are impaired, even in those with angiographically normal coronary artery.<sup>18</sup> Carotid artery intimal medial thickness (IMT) is increased in patients affected with Kawasaki disease, especially in those with coronary artery aneurysms.<sup>30</sup> Decreases of arterial compliance and distensibility, increases in aortic root size, increases in myocardial fibrosis, and alterations in the coronary artery microvasculature have been reported, although in relatively small population.<sup>7</sup> Persistence of vascular inflammation and increased oxidative stress was observed.<sup>31</sup> The clinical consequence of these findings is undetermined for patients without coronary artery lesion, although for those with persistent or regressed aneurysms, these findings indicate an increased risk of accelerated atherosclerosis, ventricular dysrhythmias, and ischemic cardiomyopathy.<sup>7</sup> Progressive localized stenosis at the site of regressed aneurysm is often observed in the late phase of Kawasaki disease. Even an angiographically normal coronary artery may developed intimal thickening, leading to accelerated atherosclerosis and premature cardiac events.<sup>30</sup> Coronary arteries of Kawasaki disease patients predispose to accelerated atherosclerosis and contribute to coronary heart disease in relatively young ages.<sup>13,18,21</sup>

## ACUTE CORONARY SYNDROME IN ADULT WITH SEQUEL OF KAWASAKI DISEASE

The growing number of adults with coronary artery lesions caused by Kawasaki disease is expected after 40 years passed since first description of this disease. Some of them have been diagnosed with Kawasaki disease in the childhood and survive into adult life, some others not known until unexpected cardiac event occurs. Acute coronary syndrome occurring in adults affected with Kawasaki disease's coronary artery lesions happen at a younger age than acute coronary syndrome in the general population. Other cardiovascular risk factors in this population were lower than common atherosclerotic acute coronary syndrome.<sup>29</sup>

In the Kawasaki disease patients, the specific nature of the Kawasaki disease-related lesions seems to strongly influence the onset of acute coronary syndrome rather than the atherosclerotic risk factors.<sup>29</sup> Accelerated atherosclerosis in affected coronary artery is responsible for development acute coronary syndrome. Atherosclerosis of patient affected with Kawasaki disease greatly differ histologically from that of common atherosclerosis.<sup>13,18</sup> Autopsy result of patients who died late after Kawasaki disease revealed calcified aneurysms, myointimal proliferation, and organizing thrombus in the coronary arteries with recanalization, whereas lipid-laden macrophages and cholesterol crystals, the hallmarks of common atherosclerosis were lack.<sup>32</sup>

This young adult population with no known previous cardiovascular history and a few cardiovascular risk factors may present with angina pectoris, myocardial infarction, ischemia-induced arrhythmia, or even sudden death.<sup>18,21</sup> Coronary angiography should be done early and the finding of the coronary arteries with proximal aneurysms with or without calcification followed by an angiographically normal distal segment should prompt anamnesis about history of Kawasaki disease in childhood.<sup>18,33</sup>

Tsuda et al.<sup>29</sup> evaluated 50 cases of acute coronary syndrome in adult patients affected with Kawasaki disease. They found that giant calcified aneurysms in the proximal part of the major branches of coronary artery were the most common culprit lesions. Thrombus formation within the aneurysm precipitated the development of acute coronary syndrome. They also suggested that even if the aneurysms underwent regression,

the risk of acute coronary syndrome remains in adult life of Kawasaki disease.

JCS working group<sup>13</sup> recommend that Kawasaki disease patients with angina pectoris, myocardial infarction, heart failure, or severe arrhythmia in adult life should be followed in the same way as patients with such conditions associated with etiologies other than Kawasaki disease. It is advised that patients should be evaluated with noninvasive techniques, such as exercise ECG, exercise or pharmacological stress myocardial scintigraphy, Holter ECG, echocardiography, magnetic resonance coronary angiography (MRCA) or multislice 3D-computed tomography (MDCT) coronary angiography, 3 to 4 times each year and coronary arteriography as appropriate.

## CONCLUSION

Young adults suffered from acute cardiac event, such as acute coronary syndrome, ischemic-associated arrhythmia and sudden death, are frequently encountered without known etiology. Coronary vasculitis due to Kawasaki disease contributes to be a risk factor in young adult population to develop acute coronary event. Sequel of Kawasaki disease of childhood is rarely recognized by internist and adult cardiologists due to lack of information in childhood medical history or undiagnosed Kawasaki disease. Better understanding of the natural history of Kawasaki disease sequel, in particular coronary artery lesions, is necessary to detect those at risk and prevent further complication.

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