—Review—

Long-Term Prognosis of Patients with Kawasaki Disease: At Risk for Future Atherosclerosis?

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Abstract

Kawasaki disease causes coronary artery lesions, such as dilatation, aneurysms, stenosis, and even occlusion in young children, and is one of the most common acquired heart diseases in developed countries. More than 10,000 new cases are reported in Japan every year. In its acute phase, severe coronary arteritis induces morphological changes in coronary arteries. Treatments for Kawasaki disease aim to eliminate coronary artery inflammation as quickly as possible to reduce the chance of causing coronary lesions. Immunoglobulin therapy with aspirin has become the standard therapy of first choice and helps attenuate coronary lesions. In addition to coronary artery disturbances in the acute phase, sclerotic vascular changes were observed in post-Kawasaki disease patients who did not have coronary lesions in the acute phase. Recent studies have revealed peripheral vasculature endothelial dysfunction in post-Kawasaki disease patients with and without coronary lesions. The risk factors for the development of atherosclerosis in adults, such as C-reactive protein, oxidative stress, and inflammatory cytokines, are also increased in the remote phase of Kawasaki disease. This morphological and functional endothelial dysfunction as Kawasaki disease vascular sequelae may suggest the early development of atherosclerosis in patients with Kawasaki disease. However, no direct evidence for this early development has been found so far. Kawasaki disease was first reported slightly more than 40 years ago. The first documented post-Kawasaki disease patients are now becoming old enough to have atherosclerosis. Some case reports suggest myocardial infarction with atherosclerotic changes in young adults who are believed to have a history of Kawasaki disease. This paper reviews Kawasaki disease from the perspective of long-term prognosis.
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Key words: Kawasaki disease, prognosis, atherosclerosis, cardiac lesion

Introduction

Kawasaki disease (KD) is the most common acquired pediatric cardiac disease in developed countries, and its etiology remains unknown. A national survey of KD has been performed every 2 years since 1970 in Japan. The most recent survey, the 19th, deals with the years 2005 and 2006. The number of new cases of KD in those years was

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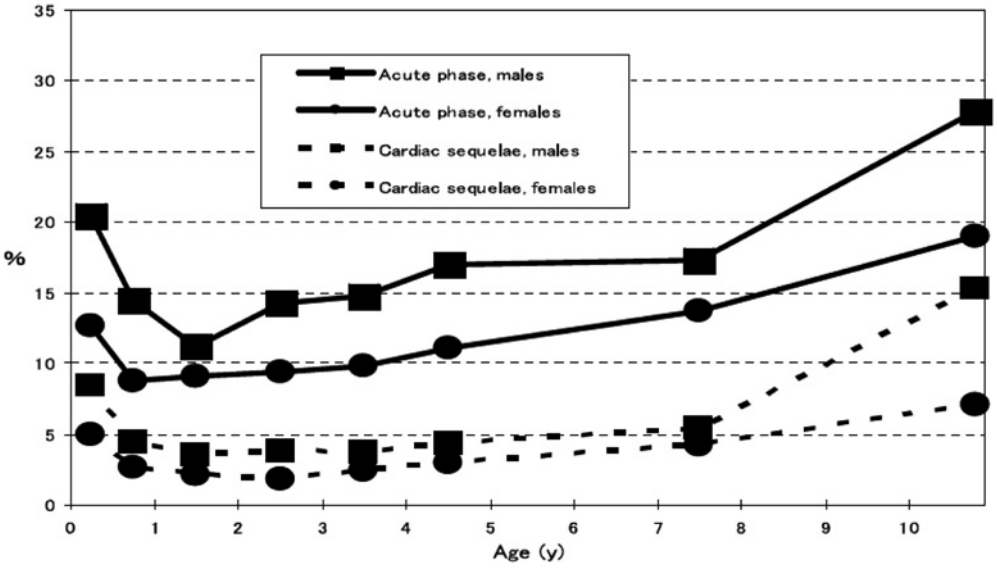

Fig. 1 Age-specific prevalence of cardiac lesions and sequelae due to Kawasaki disease in Japan in 2005－2006 (Nakamura et al., *J Epidemiol* 2008, 18 (4) 167-172)

10,041 and 10,434, respectively[1], for an annual incidence of 184.6 cases per 100,000 people (male, 209.3; female, 158.6). As of 2006, the total number of patients since 1970 was 225,682 (male, 130,827; female, 94,855). Of those patients, more than 90,000 had already reached adulthood.

The incidence of coronary lesions in the acute phase of KD has gradually been decreasing[2]. The incidence was 18.1% from 1997 through 2000 (coronary artery dilatation, 14.7%; aneurysm, 2.9%; and giant aneurysm, 0.50%), 14.8% from 2001 to 2004 (11.6%, 1.5%, and 0.35%), and 11.9% in 2005 and 2006 (10.1%, 1.5%, and 0.35%). KD sequelae, defined as coronary lesions persisting beyond 1 month after KD onset, occurred at a rate of 6.2% from 1997 through 2000 (coronary artery dilatation, 3.9%; aneurysm, 2.9%; and giant aneurysm, 0.50%), 4.5% from 2001 through 2004 (2.8%, 1.3%, 0.35%), and 3.7% in 2005 and 2006 (2.3%, 1.0%, 0.35%). These improvements can mainly be attributed to advances in intravenous immunoglobulin therapy (IVIG). In Japan, 86% of patients with KD are treated with IVIG, and a single IVIG dose of 2.0 g/kg is selected in 68% of cases. The proportions of the cardiac lesions were higher in males than in females, and among infants and old patients (**Fig. 1**). Although the incidence of coronary sequelae has gradually been decreasing, the rate of severe sequelae, such as giant aneurysms, has not been decreasing as expected. Determining how to reduce severe sequelae should be the next step in dealing with KD.

Cardiac Sequelae of Kawasaki Disease: A Natural History

Formation of Coronary Aneurysms

High echodensity of the coronary artery wall was observed in all patients with KD at a mean of 5.4 days from disease onset[3]. In the past, when IVIG was not the standard therapy and patients were treated only with aspirin, diffuse coronary artery dilatation occurred in 50% of patients with KD at a mean of 9.5 days from onset. Furthermore, diffuse coronary artery dilatation progresses to aneurysms in 28.8% of patients at a mean of 11.4 days from onset. When coronary artery dilatation resolves within 30 days from onset, the dilatation is called “transient dilation”. Coronary lesions that persist beyond 30 days from onset are considered KD sequelae. **Table 1** shows the coronary aneurysm classification in Japan.

Inflammatory cells invade the intima and destroy the internal elastic lamina and continue to infiltrate the tunica media. With inflammatory cell invasion from the adventitia, panvasculitis develops. The internal elastica and external elastica become

Table 1

(a) Classification of coronary aneurysms

1) Small Aneurysm (ANs) or Dilatation (Dil): inside diameter of regional coronary artery is less than 4 mm, or less than 1.5 times wider compared to adjacent vasculature in patients over 5 years of age.
2) Medium-sized Aneurysm (ANm): inside diameter is greater than 4 mm but less than or equal to 8 mm, or is 1.5 to 4.0 times wider compared to adjacent vasculature in patients over 5 years of age.
3) Giant Aneurysm (ANl): inside diameter is greater than 8 mm, or is more than 4 times wider in patients over 5 years of age.

(b) Classification of Severity

Coronary artery lesion severity was classified into five classes below, according to echocardiogram or coronary artery angiogram results.

1) No dilated coronary artery lesion.
2) Transient coronary artery dilatation in acute phase: a case of coronary artery dilatation is restored to normal within 30 disease days.
3) Regression: small to giant aneurysm persists beyond 30 disease days and returns to normal within one year from onset of the disease. (Coronary artery stenosis group cases excluded.)
4) Residual aneurysm: aneurysm persisted beyond one year from onset. (Coronary artery stenosis group cases excluded.)
5) Coronary artery stenosis: a case of coronary artery stenosis was observed by coronary artery angiogram.
   5-1) Coronary artery stenosis without myocardial ischemia
   5-2) Coronary artery stenosis with myocardial ischemia

Reference materials: specific comments are added to coronary artery lesion severity classes when a case has more than moderate valvular disease, heart failure, or severe arrhythmia.

fragmented, and when aortic blood pressure becomes unbearably high, aneurysm formation begins[4]. Histopathological investigations have shown 5 stages in the morphogenesis of arteritis: 1) endothelial degeneration and increased vascular permeability; 2) edema and degeneration of the media; 3) necrotizing panarteritis; 4) granulation formation; and 5) scar formation[5]. Aneurysm formation is likely to occur at the coronary artery branches, where atherosclerotic lesions are also likely to occur[6]. Reducing shear stress in aneurysms and in coronary artery branches is considered to be a mechanism facilitating aneurysm formation[7]. Furthermore, metalloproteinase (MMP)-9 expression not accompanied by an increase in the tissue inhibitor of metalloproteinase (TIMP)-1 contributes greatly to the development of aneurysms[8].

IVIG therapy contributes significantly to the reduction of cardiac sequelae and has becomes the universal standard treatment for KD[9–12]. The mechanism for the effectiveness of IVIG remains unknown; however, even in cases with positive responses to IVIG, aneurysms still occasionally form. Echocardiography should be performed at around the 30th disease day to check for KD sequelae.

Fate of Coronary Aneurysms

Regression

Most aneurysms tend to decrease in size. When an aneurysm disappears and the coronary artery looks normal, this is called "regression"[13]. Small- to medium-sized aneurysms are likely to regress within 1 to 2 years after disease onset. The frequency of this regression is 32% to 50%[14,15]. Regression is mainly the result of smooth muscular cell infiltration and proliferation in the intima[16]. Sequential coronary angiography performed 10 to 20 years after regression shows no significant stenosis[13,17]. Cases showing regression are supposed to be considered cured, and follow-up may be discontinued. However, recent reports confirm regional stenosis has occurred at regions of regression in 3 of 210 cases 8 to 10 years after disease onset[18]. In addition to morphological changes such as intimal thickening[4,18,19], reduced dilatation ability[18] and abnormal endothelial cell function[20,21] have been reported at regions of regression. Furthermore, the possibility of

atherosclerosis developing has also been suggested[22].

Occlusion

Occlusion is often observed in medium-sized or larger coronary aneurysms. Suzuki et al. have reported that 16% of coronary aneurysms are occluded at follow-up, 78% of which became occluded within 2 years from onset[23]. Whereas acute myocardial infarctions and sudden deaths have been caused by coronary artery occlusion, two-thirds of patients with occlusion have no symptomatic episodes[23]. This is a characteristic finding of KD which is consistent with histological findings, such as recanalization and well-developed collateral arteries[24].

Revascularization

Neovascularization after occlusion is called segmental stenosis. Segmental stenosis has been observed in 15% of patients with KD sequelae, 90% of which occurred in the right coronary artery[23]. The right coronary artery is occluded or revascularized more easily than the left coronary artery. Vessels revascularized after total thrombotic occlusion express vascular growth factors, which suggests that active remodeling continues in the remote phase of KD[25].

Regional Stenosis

Suzuki et al. have reported that severe regional stenosis was present at coronary angiography in 12% of 200 patients[26]. They found that regional stenosis was especially significant in the territory of the left anterior descending artery (LAD). Another group has reported regional stenosis in 4.7% of 594 patients with KD after 10 to 21 years[27]. Regional stenosis usually occurs in both the inflow and outflow shoulders of the aneurysm. Regional stenosis is caused mainly by inward luminal intimal thickening. Vascular growth factor expression is observed in vascular smooth muscle cells and microvasculature at stenosis site, which suggests active vascular remodeling is still ongoing even in the remote phase of KD[25]. Large aneurysms tend to lead to stenosis. However, even small aneurysms, such as one of 5.6 mm, lead to stenosis after a long follow-up period[15]. Intravascular Ultrasound Scope (IVUS) showed the possibility of developing stenosis in the coronary artery with intimal thickening over 4 mm[28].

Coronary Arteries without Aneurysms

Coronary arteries that appear normal from the onset of KD have been regarded as normal, so far. However, some reports have stated mild-to-moderate intimal thickening has been observed in coronary arteries without aneurysms[16,18]. A considerable amount of controversy remains surrounding the issue of whether a history of KD itself is a risk factor for future atherosclerosis.

The Long-Term Prognosis of KD

Only 40 years have passed since KD was first reported by Kawasaki[29]. Because KD mainly afflicts infants or young children, there are too few post-KD patients for proper cardiovascular investigations. One of the most conceivable issues for the long-term prognosis of KD is that the disease may represent a risk factor for atherosclerosis. KD is characterized by severe systemic vasculitis, and the post-inflammatory vasculature may not return to completely normal tissues. Because atherosclerosis is proven to be an inflammatory disorder[30], many similarities have been found in the status post-KD patients. Negro et al[31]. have reported 2 cases of acute coronary disease in young adults who had KD more than 20 years earlier. Coronary artery sequelae of KD, such as aneurysms, were not detected. Both cases were believed to be caused by atherosclerosis. However, there is no direct evidence demonstrating that KD represents a risk factor for atherosclerosis.

We have stated that typical intimal thickening in KD aneurysms is a result of active vascular remodeling. Intimal thickening is also observed in patients with KD who have normal-appearing coronary arteries[4,16]. Severe coronary arteritis denuded coronary endothelial cells at the site of aneurysm[31], but the endothelial cells themselves recovered within a few years[33]. However, recovered endothelial cells were deficient in physiological functional proteins, such as endothelial nitric oxide synthase (eNOS)[33]. The function of recovered

endothelial cells is questionable. In addition to intimal thickening in coronary lesions in patients with KD, vascular findings similar to atherosclerosis, such as vascular senescence[33] and expression of adhesion molecules[32,33] and growth factors[25,34], suggest that KD is a risk factor for atherosclerosis. In this article, we reviewed the long-term prognosis of KD vasculature from the viewpoint of its possible relationship with atherosclerosis.

The Importance of Endothelial Dysfunction for Atherosclerosis Development

Ross outlined a response-to-injury hypothesis for the development of atherosclerosis[30]. In this theory, he suggested endothelial injury and endothelial dysfunction were the keys to atherosclerosis development. Inflammatory reaction is generated by endothelial injury and induces endothelial dysfunction. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified low-density lipoprotein (LDL) cholesterol; free radicals caused by cigarette smoking, hypertension, diabetes mellitus and genetic alterations; elevated plasma homocystine concentrations; and infectious microorganisms, such as herpes viruses or *Chlamydia pneumoniae*; or combinations of these or other factors[30]. Endothelial dysfunction that results from injury leads to compensatory responses that alter the normal homeostatic properties of the endothelium. Thus, the different forms of injury increase the adhesiveness of the endothelium to leukocytes or platelets and increase its permeability. The injury also induces the endothelium to have procoagulant instead of anticoagulant properties and to form vasoactive molecules, cytokines, and growth factors[30]. Therefore, endothelial injury and dysfunction initiate the reactions for atherosclerosis progression, such as the migration and proliferation of smooth muscle cells, intimal thickening, macrophage invasion, foam cell transformation, deposition of oxidized LDL, and, finally, atherosclerotic plaque formation.

Previous studies of KD focused mainly on the morphological changes of coronary arteries. Recently, vascular functional studies of KD have been undertaken and there is now evidence of endothelial dysfunction even many years after the onset of KD. The post-KD vasculature has many similarities with atherosclerosis. We are introducing what is being discussed surrounding the issue of KD vasculature a long time after disease onset.

Vascular Elasticity

It is well known that vascular stiffness is increased in atherosclerotic vasculature. Vascular elasticity is degraded by endothelial dysfunction, intimal thickening, and by an increase in the vascular wall extracellular matrix. The loss of vascular elasticity is estimated to be a poor response to a vascular dilator. The coronary artery response to acetylcholine or isosorbide has been well documented as a marker for endothelial dysfunction. Isosorbide induces dilatation of both arteries and veins in an endothelium-independent manner. In patients with KD who have normal coronary arteries, coronary artery dilatation induced by isosorbide is no different from that in healthy persons. However, poorer coronary artery dilatation was noted according to the severity of coronary artery sequelae[17,35]. On the other hand, acetylcholine dilates arteries in an endothelium-dependent manner. When the endothelium is injured, the coronary artery shows constriction by acetylcholine, which indicates endothelium dysfunction. The reaction to acetylcholine of normal-appearing coronary arteries in patients with KD is equivalent to that of the control. However, the response to acetylcholine infusion of a coronary artery with a KD aneurysm or stenosis or both is poor dilatation or even constriction[17,20,21].

Noninvasive evaluations of vascular elasticity have also been well documented. Pulse wave velocity (PWV) and percentage change of flow-mediated dilatation (%FMD) are representative studies for evaluating arterial stiffness. The PWV is simple to measure and is a good biomarker for the risk of atherosclerosis in adults[36]. The PWV indicates the transit time required for a pulse to travel from the brachial artery at the elbow to the radial artery at the wrist. The PWV is related to the square root of the elastic modulus, according to the Moens-Korteweg equation[37]. The stiffer the artery becomes,

the faster the PWV will be. There are several reports that show PWV is especially high in patients with KD who have coronary aneurysms[38–41]. However, PWV does not differ significantly between patients with normal-appearing coronary arteries and healthy persons.

The %FMD reflects endothelial NO-dependent vasodilatation. The simulation for %FMD is provided by reactive hyperemia in the brachial artery with a cuff on the forearm inflated to greater than the systolic blood pressure for 5 minutes. A longitudinal section of the brachial artery is scanned 2 to 5 cm above the elbow with 2-dimensional ultrasonography. The diameter of the brachial artery at rest and immediately after 5 minutes of blood flow occlusion is evaluated, and the percent change of the diameter is calculated. Decreased %FMD reflects endothelial cell dysfunction, and a significant decrease in %FMD is a common feature in adult atherosclerosis[42]. Decreased %FMD in patients with KD has also been reported by multiple facilities[40,43,44]. Decreased %FMD was not found to correlate with the features of acute KD illness[44] but is related to the severity of coronary aneurysm[40,43].

Increased Carotid Intima-Media Thickness

Intima-media thickness (IMT) has been shown to reliably indicate the presence of atherosclerosis. IMT is determined with 2-dimensional ultrasonography of the carotid artery. The thicker the IMT, the higher the risk of atherosclerosis becomes. The IMT is also greater in patients with KD[39,45,46], and the IMT correlates with the severity of aneurysms in KD.

Above those reports we reviewed so far, claimed that these poor vascular elasticity findings in KD patients suggested a persistence of endothelial dysfunction, and the possibility for a future early onset of atherosclerosis. However, the studies suggesting negative findings of IMT or %FMD or both in patients with KD have also been reported[17,47].

Dyslipidemia

One of the strongest risk factors for atherosclerosis is dyslipidemia. Higher levels of LDL cholesterol, triglyceride, and total cholesterol, along with a lower level of high-density lipoprotein (HDL) cholesterol are strong cardiovascular risk factors for atherosclerosis. Dyslipidemia has also been reported in patients with KD[38,39]. However, others[40,46,47] did not confirm dyslipidemia in patients with KD with or without overt coronary artery sequelae well beyond the time that the clinical disease had been resolved. Intriguingly, invaded macrophage in intima, which is the key player in atherosclerotic plaque formation, was not detected in coronary arteries in KD patients 3 to 12 years after onset[25,33]. Therefore, it is not certain that the dyslipidemia in KD patients causes a higher risk of atherosclerosis than in other people. However, there were not enough data of KD patients afflicted over a decade ago. Epidemiologic studies among elderly people are necessary for discussing the risk of KD for dyslipidemia and atherosclerosis.

Persisting Vascular Inflammation and Increased Oxidative Stress

Atherosclerosis is fundamentally an inflammatory disorder[30]. Inflammatory biomarkers, such as C-reactive protein (CRP)[48,49], myeloloperoxidase (MPO)[50,51], or Pentraxin (PTX)-3[52] are elevated and are counted as risk factors for atherosclerosis. In addition, CRP[53] and MPO[51] themselves promote atherosclerosis. Patients with persistent coronary artery aneurysms have been shown to have ongoing systemic inflammation years after disease onset, as evidenced by significantly elevated CRP levels in a large cohort[54]. However, a study treating CRP levels in a relatively small cohort of KD patients could not show a significant difference[40].

Several lines of evidence suggest that oxidative stress may promote endothelial dysfunction through increased production of reactive oxygen species (ROS)[55]. *In vitro* studies unequivocally demonstrate that all vascular cells produce ROS and that ROS mediate diverse physiological functions in cells[56]. Furthermore, ROS play a role in the development of vasculopathies, including atherosclerosis. There are several ways to monitor total ROS generation *in vivo*. In earlier studies, these have included the measurement of thiobarbituric acid-reacting substances in blood samples, including malonyldialdehyde (MDA), and chemically stable

substances in urine, such as F_2 isoprostanes $iPF_{2\alpha}$-III (formerly known as 8-*iso*-prostaglandin $F_{2\alpha}$). Because MDA is a byproduct of cyclooxygenase (COX) turnover and $iPF_{2\alpha}$-III is somewhat formed by COX-1 and -2, they are not strictly reflected in regional ROS generation. However, they are regarded as good *in vivo* biomarkers as a quantification of basal ROS generation in many diseases. An increased level of $iPF_{2\alpha}$-III is associated with atherosclerosis risk factors, such as hypercholesterolemia[57], cigarette smoking[58], diabetes mellitus[59], renovascular hypertension[60], and hyperhomocysteinemia[61]. Urinary $iPF_{2\alpha}$-III is increased long after the onset of KD[62], as well as after acute phase KD[63]. Cheung et al. revealed significantly higher serum levels of MDA and hydroperoxides in children long after KD onset[64].

Histological Examinations

Histological examinations of atherosclerotic plaque have been well documented. Besides morphologic changes, such as intimal thickening and atherosclerotic plaque formation, characteristic features of atherosclerosis are classified as follows: a decrease in physiological functional substances such as eNOS; macrophage invasion and foamy cell transformation; LDL oxidation; and increased expression of growth factors, adhesion molecules, chemokines and cytokines. Among these histological findings, similarities and differences in KD coronary arteries have been determined. Inflammatory cell invasions, which suggest persisting coronary artery vasculitis, were not detected in coronary arteries many years after the onset of KD[25,32,33]. Takahashi et al. reported typical atherosclerotic plaque in a young adult, strongly suspecting a history of KD 19 years earlier[16]. Atherosclerotic plaque was determined in culprit lesion of acute coronary syndrome in KD patients afflicted 30 years previously[31]. However, significant macrophage infiltration or foamy cell formation was not observed in KD coronary arteries around ten years after the onset of KD[25,33,34]. Even the fatty streak, one of the earliest findings in atherosclerosis, was not detected in KD coronary arteries[25]. The few macrophages and the lack of lipid deposition were major differences between adult atherosclerosis and coronary arteries less than 10 years after the onset of KD. Therefore, a study of coronary arteries more than a decade after being afflicted with KD is greatly needed.

Other features of atherosclerosis were detected in KD coronary arteries with minor differences. The coronary artery endothelium was denuded in the acute phase of KD aneurysm[32] and recovered without the expression of functional proteins such as eNOS[33]. Growth factor expressions, transforming growth factor (TGF) β1, platelet-derived growth factor (PDGF)-A, basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF), were observed on smooth muscle cells in intima at coronary lesions[25,34]. The adhesion molecule vascular cell adhesion molecule (VCAM)-1 was mainly expressed only in neovasculature in acute phase KD[32], and was also identified on the recovered endothelium of KD aneurysms[33]. Growth factors and adhesion molecules were mainly expressed in the vaso vasorum and in neoangiogenesis in KD patients. On the other hand, these growth factor and adhesion molecule expressions were mainly admitted around intimal plaque in cases of atherosclerosis. Fukazawa et al. reported that vascular senescence increased in KD aneurysms[33]. The findings of vascular senescence, detected in the increased β-galactosidase activity and closely associated with atherosclerosis[65,66], include increased adhesion molecules and pro-inflammatory cytokines or chemokines, as well as a reduction of normal physiological vascular proteins, such as eNOS or prostacyclins. Their senescence findings in KD patients were severe in the vasculature of vasa vasorum as well as in intimal endothelial cells, which were thought to be unique to KD and different from that of adult atherosclerosis lesions. While adult atherosclerosis progression originates on the intimal side of the arteries, the atherosclerotic change of the KD aneurysm may develop from the adventitial vasa vasorum[33].

Experimental Coronary Arteritis Facilitates the Development of Atherosclerosis

Animal models of coronary arteritis showed a history of arteritis can be a risk factor for

atherosclerosis development. Allergic coronary arteritis in rabbits induced by serial horse serum injections showed typical panarteritis: inflammatory cell invasion of both sides from intima and adventitia, medial edema, and destruction of internal elastic lamina[67]. Intimal thickness with the small muscle cell (SMC) persisted even in the chronic phase, when inflammatory cells have subsided. When a high fat diet was being fed to this allergic arteritis rabbit model, typical atherosclerotic plaque appeared significantly[67]. This finding suggested post-arteritis tissue may more easily develop atherosclerotic changes.

Summary

We reviewed the problems of coronary lesions in acute phase KD as well as the possibility of early atherosclerosis long after KD onset. The risk factors for atherosclerosis have already appeared in the vasculature of patients with a history of KD. The major difference so far is the lack of lipid deposits and typical atherosclerotic plaque in KD vasculature. However, it is still too early to obtain dependable data, because most of the patients studied thus far were less than 10 years from the onset of KD. Only some case reports have suggested definite pathological findings of atherosclerosis in young adult patients with KD histories. Nonetheless, patients with a history of KD should be more careful to reduce the risks of atherosclerosis by staying healthy, dieting, exercising, and refraining from smoking. It has been over 40 years since KD was discovered and the earliest patients have only just reached the potential age for atherosclerosis. Reliable epidemiologic data are expected to appear soon.

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