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In 1997, Bradway and Drezner [1] reported the case of a 43-year-old man, with a history of Kawasaki's disease (KD), surgically treated for aneurysms of the common femoral and popliteal arteries; the clinical presentation consisted of ischemia consequent to thrombosis of the popliteal aneurysm; at the age of 17, the patient had myocardial infarction, and multiple coronary aneurysms were detected; after 26 years, echocardiography did not show any sign of coronary aneurysm. This case underscores the problem of the development of peripheral arterial aneurysms in post-KD patients, highlighted by the title of the paper [2] "When Children with Kawasaki Disease Grow Up..." published on the American Journal of Cardiology in 2009.

In 1967, Kawasaki [3] reported 50 cases of an acute febrile mucocutaneous lymph node syndrome in children. Kato et al. [4, 5], after some years, put into evidence the frequent occurrence of coronary aneurysms in affected infants and young children, identifying the underlying pathologic mechanism of the disease in a systemic vasculitis affecting small- and medium-sized arteries, with subsequent dilation and aneurysm formation. The systemic nature of KD vasculitis was documented through whole body examination [6, 7]. The cause of KD is unknown: an

infectious agent, likely entering through the lung, is suspected on the basis of clinical, epidemiological, and pathological evidences [8]; a genetic susceptibility is suggested [9].

KD is particularly frequent in Japan, with more than 10,000 new patients/year [10]; in 2012, an incidence of about 265/100,000 was registered in infants and children aged 0–4 years [11]. About 70% of the cases manifest in subjects aged less than 3 years, with a peak incidence at 1 year [12].

KD rarely affects adults: Dauphin et al. [13] reported six cases and found about 60 in the literature.

Diagnosis of KD relies on the clinical observations of five of the following signs [14]:

- Fever for 5 days or more
- Bilateral conjunctival congestion
- Changes in the lips and oral mucosa: reddening of the lips, strawberry tongue, and diffuse infection of the oral and pharyngeal mucosa
- Polymorphous exanthema
- Initial reddening with dermal induration of hand palms and foot soles, followed, in convalescence, by membranous desquamation of the tip of fingers and toes
- Acute, non-purulent, cervical lymphadenomegaly

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If dilation or aneurysms of the coronary arteries are observed, the presence of four of the above signs is considered sufficient for diagnosis.

Based on light and electron (transmission) microscopy findings, the nature of KD vasculitis is described through the occurrence of three linked processes [8]:

1. Self-limiting necrotizing arteritis: This begins and ends within the first 2 weeks from the onset of fever; it consists on a neutrophilic process starting at the endothelial level and extending toward the adventitia, causing sacular aneurysm which can thrombose or rupture.
2. Subacute/chronic vasculitis: This can begin as early as the former but can occur and persist for months or years; it begins at the adventitial or periadventitial level and progresses inward, variably damaging the wall. Arterial dilation takes place, and according to the severity of the process, it may regress or persist as fusiform dilation or frank aneurysm.
3. Luminal myofibroblastic proliferation, from medial and adventitial smooth muscle cells: This may lead to stenosis or thrombosis in the mild/moderate forms of subacute/chronic vasculitis.

The history and course of KD changed when a specific therapy was defined [15, 16] consisting of aspirin and intravenous gamma globulin administered within 10 days from the disease onset; coronary aneurysms developed in 20–25% of untreated patients [17, 18]; timely treatment would reduce to 3–5% the occurrence of such heavy complication [19]. However, it must be kept in mind that the diagnosis of KD is missed in several cases [2] and that about 15% of the patients are not responders to the standard therapy [16]. Coronary artery ectasia has been observed in more than 50% of treated patients [20] with complete resolution during the first year of follow-up.

Imaging studies may show regression of coronary aneurysms, the lumen returning to normal size [15]; this is attributed to myointimal hyperplasia producing thickening of the intima in the

absence of massive thrombus [21]; but not all aneurysms regress, and their persistence may be accompanied by the development of stenosis at the outlet.

Kato et al. [22] performed an extended follow-up, often inclusive of repeated coronary angiography, of 594 KD children; of the coronary aneurysms detected in 146, almost 50% regressed within 1–2 years; however, none of the 26 patients with initially giant (>8 mm) coronary aneurysms did show any regression, and development of stenosis was observed in 12 of them (46%). Of the 448 patients with initially normal coronary angiography, none developed abnormal cardiac findings. Thirteen children with giant coronary aneurysms (2.2% of the entire cohort) developed 39 systemic aneurysms, mainly involving axillary and hypogastric arteries.

Infants aged less than 7 months look particularly susceptible to the development of coronary and mid-artery aneurysms [23]; the 11 cases of peripheral gangrene collected by Tomita et al. belong to this age group [24]: 9 patients had giant coronary aneurysms and 8 had peripheral aneurysms.

Several reports on non-coronary arterial aneurysms in KD are found in the literature: abdominal aorta [25, 26]; common iliac artery [27, 28], hypogastric artery [28, 29], subclavian-axillary arteries [24, 30–32], brachial artery [33], hepatic artery [34, 35], and cerebral arteries [36]. Multiple aneurysms concomitant with coronary aneurysms have been described [37–39]. Lesions observed in peripheral arteries are similar to those found in coronary arteries [40], and the evolution of peripheral aneurysms follows the same course of that observed for coronary aneurysms. Miyake et al. [41], in an 8-month-old infant, observed dilation of the terminal aorta on the 27th day from disease onset, with subsequent apparently full regression after 18 days. Regression of peripheral aneurysms is often observed at a 6–12-month follow-up [42], but not all aneurysm regress, and they may remain unchanged for years (like the abdominal aortic aneurysm followed up for 7 years by Fuyama et al. [26] in a child affected with KD at the age of 2 months) or undergo thrombosis [21, 43].

Hoshino et al. [44] studied retrospectively the fate of systemic aneurysms in 20 KD patients, all presenting at least a couple of symmetric peripheral aneurysms and 16 having multiple aneurysms, totaling 107 aneurysmatic lesions, mainly located at the brachial or iliac level; the age at the onset of KD ranged 1–20 months and the age at the latest angiographic study ranged 2–26 years; the mean period of retrospective observation was 18 years. All patients had coronary aneurysms, mostly (19/20) of giant size. As a result, 51% of aneurysms regressed, while stenotic lesions developed in 25%.

For the purpose of the present review, KD is an intriguing disease, as no popliteal aneurysm is mentioned in the different reports, but for the case described by Bradway and Drezner [1], in which a microscopy study is lacking. The latter, however, may represent a warning to investigate the occurrence of childhood KD in young or young adult patients with popliteal aneurysm and no (apparent) signs of atherosclerosis. In general, two questions deserve an answer [45] regarding persons affected with KD in childhood:

1. Whether long-term cardiovascular sequelae may be expected after KD
2. If KD arteritis may represent a premise for accelerated atherosclerosis

According to the Japanese Circulation Society [46], eventual late cardiovascular symptoms begin to appear 20 years after the onset of the disease.

Adverse cardiac events have been the object of careful investigation. Coronary dysfunction was detected both in cases of persisting coronary aneurysms [47] and in cases of only transient coronary dilatation [48]. Yamakawa et al. [49] observed a paradoxical vasoconstriction in response to intracoronary acetylcholine long after KD and suggested a prolonged endothelial dysfunction; KD may be considered as a harbinger of early onset of coronary disease in adults [50]. Of 154 cardiovascular deaths in persons under 35 years, 2 (1.3%) were related to KD in childhood [51]. Kato et al. [52], reviewing the registries of 354 hospitals in Japan, found that,

out of 130 adults with coronary aneurysms, 2 presented a definite and 19 a suspected history of KD. Burns et al. [53] studied retrospectively 74 patients, aged 12–39 years, who presented cardiac problems, presumed to be late consequences of KD: coronary aneurysms were found in 93.2% and coronary stenosis in 66.1%. Giant coronary aneurysms developed during the acute phase of KD appear linked to a bad long-term prognosis [54].

The eventual late impact of KD on systemic arteries is rather undefined, but some clinical reports should, at least, arise an alert. Wakisaka et al. [55] described a young adult submitted, at 33 years, to grafting procedure for abdominal aortic aneurysm; the patient had been submitted to aortocoronary bypass grafting at 19 years and was probably affected with KD at 14 years of age. Studies with PET [56] detected persisting arteritis long after KD. Late endothelial dysfunction was observed by some authors [57, 58], not by others [59]. Long-term (post-inflammatory) increase of arterial stiffness was noticed [60] also in cases without apparent coronary lesions during the acute phase [61].

In conclusion, the long-term sequelae of KD on peripheral arteries are not yet defined, and studies on larger numbers of individuals with a history of childhood KD are needed. These evaluations can be complicated by the fact that KD is still relatively poorly recognized in many countries so that diagnosis can be missed in several cases; as well, the frequent apparently benign course of the disease may obscure the need for a close and dedicated follow-up.

References

1. Bradway MW, Drezner AD. Popliteal aneurysm presenting as acute thrombosis and ischemia in a middle-aged man with a history of Kawasaki disease. *J Vasc Surg.* 1997;26:884–7.
2. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up. Myocardial and vascular complications in adulthood. *J Am Coll Cardiol.* 2009;54:1911–20.
3. Kawasaki T. Acute febrile mucocutaneous lymphode syndrome with lymphoid involvement, with specific desquamation of the fingers and toes in children:

- clinical observations of 50 patients. *Jpn J Allergy*. 1967;16:178–222.
4. Kato H, Koike S, Yamamoto M, Ito Y, Yano E. Coronary aneurysms in infants and young children with the mucocutaneous lymph node syndrome. *J Pediatr*. 1975;86:892–8.
 5. Kato H, Koike S, Tanaka C, Yokochi K, Yoshioka F, Takeuchi S, Matsunaga S, Yokoyama T. Coronary heart disease in children with Kawasaki disease. *J Jpn Circ*. 1979;43:469–75.
 6. Amano S, Hazawa F, Kubagawa H, Tasaka K, Haebara H, Hamashino Y. General pathology of Kawasaki disease. On the morphologic alterations corresponding to the clinical manifestations. *Acta Pathol Jpn*. 1980;30:681–94.
 7. Landing BH, Larson EJ. Pathological features of Kawasaki disease (mucocutaneous lymphnode syndrome). *Am J Cardiovasc Pathol*. 1987;1:218–29.
 8. Orenstein JM, Shulman ST, Fox LM, Baker SC, Takahashi M, Bhatti TR, Russo PA, Mierau GW, de Chadarévian JP, Perlman EJ, Trevenen C, Rotta AT, Kalelka MB, Rowley AH. Three linked vasculopathic processes characterize Kawasaki disease: a light and transmission electron microscopic study. *PLoS One*. 2012;7(6):e38998.
 9. Dergun M, Kao A, Hauger SB, Newburger JW, Burns JC. Familial occurrence of Kawasaki syndrome in North America. *Arch Pediatr Adolesc Med*. 2005;159:876–81.
 10. Nakamura Y, Yashiro M, Uehara R, Oki I, Kayaba K, Yanagawa H. Increasing incidence of Kawasaki disease in Japan: nationwide survey. *Pediatr Int*. 2008;72:134–8.
 11. Makino M, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, Kojo T, Uehara R, Kotani K, Yanagawa H. Descriptive epidemiology of Kawasaki disease in Japan, 2011–2012: from the results of the 22nd nationwide survey. *J Epidemiol*. 2015;25:239–45.
 12. Takahashi K, Oharaseki T, Yokouchi Y, Hiruta N, Naoe S. Kawasaki disease as a systemic vasculitis in childhood. *Ann Vasc Dis*. 2010;3:173–81.
 13. Dauphin C, Motreff P, Souteyrand G, Laurichesse M, Gourdon F, Lesens O, Lamaison D, Beytout J, Cassagnes J, Lusson JR. La maladie de Kawasaki est aussi une maladie de l'adulte: à propos de six observations. *Arch Mal Coeur Vaiss*. 2007;100:439–47.
 14. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, Ishii M, Harada K, Kawasaki Disease Research Committee. Revision of diagnostic criteria for Kawasaki disease (the 5th revised edition). *Pediatr Int*. 2005;47:232–4.
 15. Kato H, Ichinose E, Yoshioka F, Takechi T, Matsunaga S, Suzuki K, Rikitake V. Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long term follow-up study. *Am J Cardiol*. 1982;49:1758–66.
 16. Furusho K, Nakano H, Shinomiya K, Tamura T, Manabe Y, Kawarano M, Baba K, Kamiya TY, Kiyosaw N, Hayashidera T, Hirose O, Yokoyama T, Baba K, Mori C. High-dose intravenous gammaglobulin for Kawasaki disease. *Lancet*. 1984;2:1055–8.
 17. Suzuki A, Kamiya T, Kuwahara N, Ono Y, Kohata T, Takahashi O, Kimura K, Takamiya M. Coronary arterial lesions of Kawasaki disease: cardiac catheterization findings of 1100 cases. *Pediatr Cardiol*. 1986;7:3–9.
 18. Jin B, Feng X-Y. Dual-source CT imaging of multiple giant coronary and axillary aneurysms in a child with Kawasaki disease. *Eur Rev Med Pharmacol Sci*. 2014;18:1969–72.
 19. Newburger JW, Takahashi M, Burns JC, Betser AS, Gheng KJ, Duffy E, Glode MP, Mason WH, Reddy V, Sanders SP, Shulman ST, Wiggins JW, Hicks RW, Fulton DR, Lewis AB, Leung DYM, Colton T, Rosen FS, Melish ME. The treatment of Kawasaki syndrome with intravenous gamma globulin. *N Engl J Med*. 1986;315:341–7.
 20. Morales-Quispe A, Espinosa-Zavaleta N, Caballero-Caballero R, Garcia Lopez JJ, Rodriguez-Quezada JM, Betanzes-Rodriguez L. Enfermedad de Kawasaki: evolucion y complicaciones cardiovasculares en niños. *Rev Med Inst Mex Seguro Soc*. 2011;49:295–300.
 21. Sasaguri H, Kato H. Regression of aneurysms in Kawasaki disease: a pathological study. *J Pediatr*. 1982;100:225–31.
 22. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. *Circulation*. 1996;94:1379–85.
 23. Bachiri A, Francart C, Godart F, Brevière GM, Vaksman G, Martinot V, Rey C. Ischémie de la main révélant une maladie de Kawasaki. *Arch Pédiatr*. 2000;7:1307–10.
 24. Tomita S, Chung K, Mas M, Gidding T, Shulman ST. Peripheral gangrene associated with Kawasaki disease. *Clin Infect Dis*. 1992;14:121–6.
 25. Canter C, Bower RJ, Strauss A. Atypical Kawasaki disease with aortic aneurysm. *Pediatrics*. 1981;68:885–8.
 26. Fuyama Y, Hamada R, Uehara R, Yano I, Fujiwara M, Matuba M, Kawamura K, Nonaka Z, Maekawa K. Long-term follow-up of abdominal aortic aneurysms complicating Kawasaki disease: comparison of the effectiveness of different imaging methods. *Acta Paediatr Jpn*. 1996;38:252–5.
 27. Saga T, Shirohara H, Shinohara T. Surgical treatment for coronary and iliac arterial lesions in a case of Kawasaki disease. *Thorac Cardiovasc Surg*. 1995;43:57–9.
 28. Casadonte JR, Perez VM, Stapleton G, Crawford MM, Jacobs JP, Cooper DS, Dadlani GH. Magnetic resonance angiography detection of vascular aneurysms in patients with Kawasaki disease and coronary artery aneurysms. *World J Pediatr Congenit Heart Surg*. 2010;1:393–6.
 29. Pires A, Sousa G, Castela E. Coronary and systemic aneurysms in an infant with Kawasaki disease. *Pediatr Cardiol*. 2009;30:568–9.

30. Wilson DA, Luckstead E, Stuemky JH. Echocardiographic findings in a fatal case of Kawasaki's disease. *Am J Dis Child.* 1979;133:1028-30.
31. Fukushige J, Nihill MR, McNamara DG. Spectrum of cardiovascular lesions in mucocutaneous lymph node syndrome: analysis of eight cases. *Am J Cardiol.* 1980;45:98-107.
32. Teixeira OHP, Pong AH, Vlad P. Amputating gangrene in Kawasaki disease. *CMA J.* 1982;127:132-4.
33. Cabrera ND, Sridahr A, Chessa M, Carminati M. Giant coronary and systemic aneurysms of Kawasaki disease in an infant. *Pediatr Cardiol.* 2010;31:915-6.
34. Lipson M, Ament M, Fonkalsrud EW. Ruptured hepatic artery aneurysm and coronary artery aneurysms with myocardial infarction in a 14-year-old boy: new manifestations of the mucocutaneous lymph node syndrome. *J Pediatr.* 1981;98:933-6.
35. Marks WH, Coran AG, Wesley JR, Di Pietro M, Byrne W, Bowerman R, Nolan B. Hepatic artery aneurysm associated with the mucocutaneous lymph node syndrome. *Surgery.* 1985;98:598-601.
36. Lapointe J, Nugent R, Graeb D, Robertson WD. Cerebral infarction and regression of widespread aneurysms in Kawasaki disease: case report. *Pediatr Radiol.* 1994;14:1-5.
37. Bajolle F, Jurzak P, Cohen S, Boudjemline Y. Endovascular treatment of peripheral aneurysms in Kawasaki disease. *Arch Cardiovasc Dis.* 2013;106:694-6.
38. Heran MK, Hockley A. Multiple mirror-image peripheral arterial aneurysms in Kawasaki disease. *Pediatr Cardiol.* 2011;32:670-3.
39. Ekici F, Varan B, Kokabas E, Erdogan I, Eminoglu S, Aktas D. Multiple giant aneurysms and stenosis of the coronary and systemic arteries in an infant with Kawasaki disease at the early stage of the convalescent period. *Echocardiography.* 2014;31:E147-50.
40. Masuda H, Shozawa T, Naoe S, Tanaka N. The intercostal artery in Kawasaki disease. A pathological study of 17 autopsy cases. *Arch Pathol Lab Med.* 1986;110:1136-42.
41. Miyake T, Yokoyama T, Shinohara T, Seto S, Oiki M. Transient dilatation of the abdominal aorta in an infant with Kawasaki disease associated with thrombocytopenia. *Acta Paediatr Jpn.* 1995;37:521-5.
42. Yacoe ME, Dake MD. Development and resolution of systemic and coronary artery aneurysms in Kawasaki disease. *Am J Roentgenol.* 1992;159:708-10.
43. Ames EL, Jones J-S, van Dommelen B, Posch JL. Bilateral hand necrosis in Kawasaki syndrome. *J Hand Surg Am.* 1985;10:391-5.
44. Hoshino S, Tsuda E, Yamada O. Characteristics and fate of systemic arterial aneurysms after Kawasaki disease. *J Pediatr.* 2015;167:108-12.e1-2.
45. Burns JC, Daniels LB. Assessing vascular health after Kawasaki disease: a cautionary tale. *J Am Coll Cardiol.* 2013;62:1122-3.
46. Japanese Circulation Society, Joint Research Group. Guidelines for the diagnosis and management of cardiovascular sequelae in Kawasaki disease. *Pediatr Int.* 2005;47:711-32.
47. Cicala S, Galderisi M, Grieco M, Lamberti A, Cosimi R, Pellegrini F, de Leva F. Trans-thoracic echodoppler assessment of coronary microvascular function late after Kawasaki disease. *Pediatr Cardiol.* 2008;29:321-7.
48. Furuyama H, Odagawa J, Katoh C, Iwado Y, Ito Y, Noriyasu K, Mabuchi M, Yoshinaga K, Kobayashi K, Tamaki N. Altered myocardial flow reserve and endothelial function late after Kawasaki disease. *J Pediatr.* 2003;142:149-54.
49. Yamakawa R, Ishii M, Sugimura T, Akagi T, Eto G, Iemura M, Tsutsumi T, Kato H. Coronary endothelial dysfunction after Kawasaki disease: evaluation by intracoronary injection of acetylcholine. *J Am Coll Cardiol.* 1998;31:1074-80.
50. Satou GM, Giamelli J, Gewitz MH. Kawasaki disease: diagnosis, management and long-term implications. *Cardiol Rev.* 2007;111:2119-25.
51. Shimizu C, Sood A, Lau HD, Oharaseki T, Takahashi K, Krous HK, Campman S, Burns JC. Cardiovascular pathology in 2 young adults with sudden, unexpected death due to coronary aneurysms from Kawasaki disease in childhood. *Cardiovasc Pathol.* 2015;24:310-6.
52. Kato H, Inoue O, Kawasaki T, Fujiwara H, Watanabe T, Toshima H. Adult coronary artery disease probably due to childhood Kawasaki disease. *Lancet.* 1992;340:1127-9.
53. Burns JC, Shike M, Gordon JB, Malhotra H, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. *J Am Coll Cardiol.* 1996;28:253-7.
54. McNeal DA, Fournier R, Scuccimarri R, Dancea A, Houde C, Bellavance M, Dahdah N. The fate and observed management of giant coronary aneurysms secondary to Kawasaki disease in the province of Quebec: the complete series since 1976. *Pediatr Cardiol.* 2013;34:170-8.
55. Wakisaka Y, Tsuda E, Asakura T. A young adult who had undergone coronary artery bypass grafting and abdominal aortic replacement with prosthetic vessel later after incomplete Kawasaki disease. *J Cardiol.* 2010;55:120-4.
56. Suda K, Tahara N, Honda A, Iemura M, Yoshimoto H, Kudo Y, Kaida H, Abe T, Sawada K, Akashi H, Tanaka H, Fukumoto Y. Persistent peripheral arteritis long after Kawasaki disease: another documentation of ongoing vascular inflammation. *Int J Cardiol.* 2015;180:88-90.
57. Dhillon R, Clarkson P, Donald AE, Powe AJ, Nash M, Novelli V, Dillon MJ, Dearfield JE. Endothelial dysfunction late after Kawasaki disease. *Circulation.* 1996;94:2103-6.
58. Niboshi A, Hamaoka K, Sakata K, Yamaguchi N. Endothelial dysfunction in adult patients with a history of Kawasaki disease. *Eur J Pediatr.* 2008;167:189-96.
59. McCrindle BW, McIntyre S, Kim C, Lin T, Adeli K. Are patients with Kawasaki disease at increased

- risk for accelerated atherosclerosis? *J Pediatr.* 2007;151:244–248.e1.
60. Tobayama H, Takahashi K, Fukunaga H, Matsui K, Tanaka N, Harada M, Furukawa T, Oda H, Akimoto K, Kishihiro M, Shimizu T. Analysis of arterial function in adults with a history of Kawasaki disease. *J Cardiol.* 2013;61:330–5.
61. Nakagawa R, Kuwata S, Kurishima C, Saiki H, Iwamoto Y, Sugimoto M, Ishido H, Masutani S, Senzaki H. Arterial stiffness in patients after Kawasaki disease without coronary artery involvement: assessment by performing brachial-ankle pulse wave velocity and cardio-ankle vascular index. *J Cardiol.* 2015;66:130–4.