

The histories of Kawasaki disease[☆]

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Abstract

This paper describes the historical evolution of the Kawasaki disease (KD) from a pediatric vasculitis to a clinical syndrome with a putative infectious cause. The KD clinical criteria were developed before the general acceptance of coronary artery aneurysms (CAAs) as sequelae. Later, the pediatric vasculitis labeled in 1963 as infantile polyarteritis nodosa (IPN) would be viewed as the fatal end of a KD spectrum. Research efforts that focus on identifying the KD etiologic agent(s) may be hampered by the fact that a significant number of children develop CAA without meeting the KD criteria and are therefore excluded from research protocols. In what follows, we suggest that the reluctance to adopt a broader view of the spectrum of KD results more from historical circumstance than from scientific findings.

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History can provide important insights for diagnosis and treatment as well as for understanding the pathophysiology and the search for the etiology of the Kawasaki disease (KD). Although clinicians generally view the history of medicine as useful and interesting, they rarely see its relevance for clinical research and practice. They expect a history of medicine to provide the “facts” about “what actually happened” in the past. Professional historians, on the other hand, are trained to uncover how the meanings of “facts” depend upon context. Questioning whether one can ever recapture “what actually happened,” historians learn to construct narratives based on both context and interpretation of the meaning of so-called facts. Like clinical

researchers, historians of medicine test hypotheses and acknowledge the tentative nature of their claims. From this perspective, there are “histories,” rather than one “history” of KD.

KD is named for the Japanese pediatrician Tomisaku Kawasaki, who in 1967 described 50 cases of a rash/fever illness of early childhood, including edema, conjunctival injection, redness and cracking of the lips, “strawberry tongue,” convalescent desquamation, and, sometimes, lymphadenopathy [1,2]. Kawasaki initially believed that the illness was benign and without sequelae. A history of KD will be very different if one assumes that it was, as Kawasaki claimed in 1967, a new disease, or, as Landing and Larsen [3] concluded 10 years later, that it was synonymous with infantile polyarteritis nodosa (IPN) [4]. Similarly, the KD agent or agents have their own history. If the KD agent resembles other infectious childhood rash–fever disease agents, such as Group A beta hemolytic streptococcus (GABHS) in rheumatic fever, it is possible that its ability to cause disease may have changed over the past century [5]. Although the view is widely held that KD is a spectrum that moves from benign cases to potentially

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fatal ones, Kawasaki, after whom the disease is named, initially believed that the syndrome he described was always benign, with no sequelae. Despite the dominant view to the contrary, Kawasaki remains skeptical that KD is a spectrum. Thus, the content of the historical narrative depends on which interpretation of KD one accepts. More importantly, each interpretation raises interesting and compelling questions which authorize clinicians and researchers to pursue different lines of inquiry.

For instance, in a previous publication, we have argued that placing the current KD diagnostic criteria in historical context reveals the extent to which an epidemiological instrument was transformed into a diagnostic tool [6]. As a result, treatment is often delayed for children who fail to meet the KD case definition criteria but who, nevertheless, develop coronary artery aneurysms (CAAs). Such a history calls into question reliance on an epidemiologic case definition, which was created to be very specific and exclude other rash/fever illnesses, for purposes of diagnosis and treatment, where sensitivity for the detection of children at risk for CAA is the goal [6]. It reminds clinicians that KD, despite its name, is a syndrome, whose signs must remain tentative until the etiology or pathophysiology of KD is fully elucidated. Historical investigation can also reveal why the current case definition retains its hold despite so much clinical evidence suggesting its diagnostic imperfections. This history reveals that the canonization of the KD case definition was due as much to the enshrinement of a particular historical narrative of the role of KD's discoverer, as it was informed by compelling scientific findings. Consequently, research on the etiology and mechanisms of CAA has been limited to the population that meets the KD diagnostic criteria, rather than to those who are at risk of CAA [7].

In this paper, we argue that the privileging of Kawasaki's clinical criteria eclipsed earlier work of researchers on the pathophysiology of the vasculitis, focusing instead on a concern with the putative infectious etiological agent. As a result, much remains unknown about the mechanisms of the KD cascade, while the KD etiological agent or agents remain obscure.

The signs associated with what we today call KD have varied over time as the disorder has been viewed through a variety of lenses [8,9]. Pathologists in the 1950s encountered the condition only when a child developed CAA and died, whereas pediatricians like Kawasaki and Melish and Hicks observed the illness in patients who initially appeared to have a benign disorder with no sequelae. As a result, different case definitions were constructed to identify what may have been the same syndrome at different stages and among different subsets of patients. The dominant view today is that the signs and symptoms that have been grouped together as KD represent a spectrum, in which a single cause can result in a series of different outcomes—from a self-limiting benign illness to death from CAA.

1. Infantile periarteritis nodosa (IPN)

Cases of what today is called KD may have been apparent in the 1940s, as an increasing number of autopsies and published reports of pediatric cases of periarteritis (or polyarteritis) nodosa (PN) appeared [10–13]. PN had long been recognized as a baffling condition of unknown etiology—invariably fatal and seldom diagnosed during life [14]. First [15] described in 1866, the condition typically was diagnosed at autopsy when arterial aneurysms and lesions produced by extensive infiltration of arterial walls by inflammatory cells were discovered. Arterial dilatation associated with transmural inflammation generally occurs at the points where a medium-sized muscular artery branches into smaller arteries. This arteritis is the hallmark of PN.

By the late 1940s and early 1950s, researchers increasingly challenged the view that PN was a single disease [16,17]. These studies indicated that pediatric patients displayed similar but varying pathology and histology, and that, unlike PN in adults, the vasculitis and aneurysms were generally limited to the coronary arteries [17]. Moreover, most, but not all, of the infants and children diagnosed with PN displayed a relatively consistent array of signs and symptoms that differed considerably from those in adult PN [18–21]. This evidence persuaded a number of researchers that pediatric PN should be reclassified as separate from adult PN. In 1963, Roberts and Fetterman [22] concluded that pediatric PN constituted a “constant clinical syndrome,” which included “a transient macular exanthem, transient conjunctivitis, prolonged pyrexia, cardiomegaly, congestive heart failure, electrocardiographic changes, and abnormal urinary sediment,” and they named the syndrome, “infantile periarteritis nodosa” or IPN (Table 1).

2. Nonfatal infantile periarteritis nodosa

Throughout this period, there seems to have been an increasing recognition of nonfatal cases with signs similar to

Table 1
Sign/Symptom Complex of Infantile Periarteritis Nodosa (IPN)

Clinical Manifestations
1. Prolonged/intermittent fever
2. Erythematous macules, erythema multiforme, or urticaria
3. Conjunctivitis
4. Cough/grunting or grunting respirations
5. Congestive heart failure
6. Abnormal CNS signs
7. Hypertension
8. Pericardial effusion
9. Gangrene of extremities
Laboratory Findings
1. Abnormal urinary findings
2. Chest radiogram abnormalities of lung parenchyma or cardiomegaly
3. Abnormal ECG

Source: Roberts and Fetterman [22].

the fatal cases of IPN. In a 1949 report of a 9-month-old girl who died as a result of a coronary artery aneurysm, Cleveland University Hospitals pediatricians Sinclair and Nitsch [23] wrote that the child's clinical signs resembled "a mild form of Stevens–Johnson syndrome" (SJS). Based on a review of medical literature, however, they concluded that the child had two distinct conditions. The first, SJS, accounted for her clinical signs, and the second, PN, was the proximate cause of the aneurysms that led to her death. In the postmortem discussions, one pediatrician noted that he had seen "three recent [nonfatal] cases with a similar history and similar signs and symptoms." The sign complex, he noted, "usually begins with a fever of 4–5 days duration during which time the patient becomes acutely ill." The children all presented with "a lymphadenitis, stomatitis, and conjunctivitis" followed by "an erythematous [sic] rash either morbilliform-like or even bullous in character. Signs of encephalitis, pneumonitis, and myocarditis may or may not be present." They also had rapid pulse and respiration and an elevated white blood count. Unlike the 9-month-old patient, these children "recovered without known sequelae" [24,25].

Although nonfatal cases were rarely the subject of American and European journal articles, in Japan they became the focus of medical publications. In 1960, Itoga and Yamagishi [26], pediatricians from Keio University, reported that since 1954 they had treated with steroids 20 cases of a nonfatal childhood illness they called "Mucocutaneous Ocular Syndrome" (MCOS). Their description of clinical signs resembled the reports of other nonfatal IPN cases. All of the children were between 2 months and 7 years old, with 95% less than 2 years old. All presented with fever, rash, mucosal, and ocular (conjunctival) signs. Sixty percent had diarrhea, while 35% reported vomiting and 35% had lymph node swelling. Twenty percent were reported with arthritis. None of the children were found to have any bacterial infection, and all survived without any observed sequelae. Itoga and Yamagishi [26] wrote that MCOS "is an acute febrile disease that specifically affects the skin, mucosal membrane, and eyes," and was therefore a variation of Stevens–Johnson syndrome.

The next year, Kawasaki saw his first case of a child whose clinical signs closely resembled those reported by Itoga and Yamagishi [17,27]. The patient, a 4-year-old male, recovered spontaneously from his illness and was discharged as "diagnosis unknown." Kawasaki believed that the clinical syndrome was a benign, self-limited process with no sequelae. He reported the first seven cases as "nonscarlet fever syndrome with desquamation" at a 1962 meeting of the Chiba District Pediatric Group of the Japanese Pediatric Association [28]. By 1964, he and his clinical supervisor, Fumio Kosaki, Director of pediatrics at Red Cross Hospital, had gathered 20 cases which they presented at the 15th Eastern and Central Japan Pediatric Meeting in Matsumoto [29]. Like Itoga and Yamagishi earlier, Kosaki and Kawasaki labeled these cases as

"mucocutaneous ocular syndrome." At Kosaki's urging, Kawasaki published his series of 50 patients in the *Japan Journal of Allergy* in 1967 [1].

In the 1967 paper, Kawasaki abandoned the label MCOS, arguing that the term was historically confusing and clinically nonspecific. He pointed out that MCOS had been used synonymously with Stevens–Johnson syndrome, and that different authors had used MCOS to describe varying combinations of clinical signs. Conceding that the cases reported by Itoga and Yamagishi "closely resemble ours in many aspects," Kawasaki nevertheless pointed to "important clinical differences." Most important was that twice as many of Kawasaki's patients (68%) presented with cervical lymphadenopathy.

Distinguishing his description of signs from those reported by Itoga and Yamagishi, Kawasaki argued that he had discovered a new or, at least, distinct syndrome. He named it "Pediatric Acute Febrile Mucocutaneous lymph node Syndrome," which became the acronyms MLNS and MCLS. Interestingly, the English language abstract of Kawasaki's 1967 article had a more descriptive title, one that deemphasized lymphadenopathy: "Febrile oculo-oro-acrodesquamatus syndrome with or without acute non-suppurative cervical lymphadenitis in infancy and childhood: clinical observation of 50 cases" (Table 2) [1].

Kawasaki's report led to a debate over the possible link between the syndrome he described and cardiac complications. Takajiro Yamamoto, Head of pediatrics at Tokyo's St. Luke's Hospital, was the first to suspect cardiac involvement in nonfatal cases of MCLS [30]. Like Kawasaki, he had been independently gathering cases in the late 1950s and early 1960s. In December 1966, one of his patients presented with the clinical signs that Kawasaki had described, along with a gallop rhythm associated with

Table 2
Kawasaki Sign Complex

Symptoms	Number of cases (%)
Even with the use of antibiotics, fever higher than 38 °C persists longer than 6 days	50 (100%)
Bilateral bulbar conjunctiva presents injection	49 (98%)
Erythematous rash seen particularly on bilateral palm and/or bilateral sole, but never forms vesicles	43 (86%)
Redness, dryness, erosion, cracking, sometimes bleeding and hemorrhagic scab on lips, and sometimes diffuse injection of oral mucosa and strawberry tongue; no formation of vesicles, ulcers, pseudomembrane, or aphtha	48 (96%)
Acute swelling of neck lymph node(s) equal or bigger than thumb; never develops to pyrosis	33 (68%)
Bilateral hands and feet present vasoneurogenic edema	22 (68%)
Desquamation starts from nail–skin junction of fingers and toes, mostly from the second week of disease	49 (98%)
Under 2 years of age	27 (54%)
No recurrence	50 (100%)
Resolves without intervention; no sequelae	50 (100%)

Note: No contagion between siblings observed.

Source: Kawasaki [1].

congestive heart failure. In 1968, Yamamoto and Kimura [30] published a report of 23 patients, of whom 11 (48%) had abnormalities detected by electrocardiogram. These results persuaded Yamamoto that cardiac involvement was a common feature of this syndrome. Kawasaki, on the other hand, insisted that the cardiac abnormalities described by Yamamoto were distinct from MCLS, whose course was always benign, and his position on this issue mirrored that of Sinclair and Nitsch [23], who had insisted that there was no causal connection between an antecedent rash/fever illness and subsequent coronary aneurysms.

In 1962, pathologist Ika Chen and colleagues at the Red Cross Hospital published “An autopsy case of infantile polyarteritis nodosa,” which Kawasaki concluded was not related to the syndrome he was uncovering [31,32]. In 1965, Noboru Tanaka [33], a coauthor of the Chen paper and then head of pathology at the Red Cross Hospital, performed an autopsy on a second child, whom Kawasaki had previously diagnosed with MCOS. Tanaka’s autopsy revealed coronary artery thrombosis, and “clinical diagnosis was “mucocutaneous ocular syndrome, sudden death, unknown etiology” [33]. Despite the autopsy evidence, Kawasaki published a two-part article in 1970 rejecting the association of his disease with fatal cardiac complications [34,35]. Kawasaki listed Tanaka as a contributing author, although Tanaka disagreed with the paper’s conclusion [36,37].

Thus, when the Japanese MCLS Research Committee (JRC) [38] formulated the first case definition for a national survey in 1970, MCLS was seen as an acute febrile illness with a benign outcome. The 1970 national survey included a request that clinicians report any fatal outcomes occurring in MCLS patients [36]. The result of that request was the discovery that 10 children had died suddenly from thrombosis of aneurysms [38]. This finding helped to establish coronary vasculitis as a complication of MCLS. While he accepted the finding of the JRC that vasculitis could accompany the signs of MCLS, Kawasaki remained more circumspect and ambiguous about whether such findings demonstrated that IPN was part of the MCLS spectrum [27,39–41].

3. The merger of infantile periarteritis nodosa and Mucocutaneous lymph node syndrome

Persuasive evidence linking IPN to MCLS came from Hawaii. In 1971, Eunice Larson, a pediatric pathologist at Kaula Children’s Hospital in Honolulu, performed an autopsy on a 10-month-old Japanese-American infant who died of coronary artery thrombosis [42]. Baffled by the case, Larson subsequently sent the autopsy report to her former professor, Benjamin Landing, pathologist-in-chief at Children’s Hospital of Los Angeles [43]. Landing informed Larson that in a recent trip to Japan he had learned of a syndrome described by Kawasaki that resembled her case.

In April 1973, Larson altered her diagnosis on the autopsy to “infantile coronary periarteritis disease (Kawasaki disease) with generalized necrotizing vasculitis [and] thrombosis of coronary arteries.” She attached a copy of the English abstract of Kawasaki’s 1967 article, noting on the revised report that “selected slides were reviewed by B. H. Landing, MD” who had “suggested the diagnosis” [42,44].

While Larson was communicating with Landing about her case, two of her colleagues, Marian Melish, a specialist in pediatric infectious diseases, and Raquel Hicks, a pediatric rheumatologist, had been seeing children with an unusual constellation of fever, rash, and red mucous membranes [45–47]. Like Larson’s fatal case, most of Melish and Hicks’s patients were Japanese-Americans. A combination of Landing’s letter to Larson and a visit from a Japanese physician distributing an English version of the 1972 Japanese case definition, complete with color photos, persuaded Melish and Hicks that the children they were seeing fit the syndrome described by Kawasaki [48,49]. Together with Larson, Melish and Hicks wrote an abstract concluding that their cases were indeed MCLS as described in Japan and that the syndrome could, as Larson’s case demonstrated, result in coronary artery aneurysms and death [50,51].

A similar conclusion was reached by Fetterman, who in 1963 [22] had joined with Roberts in classifying IPN as a distinct pediatric illness. In a commentary in the 1974 *Pediatrics* issue that included Kawasaki’s first English language description of MCLS, Fetterman and his colleague Yoshie Hashida wrote that “careful study of the details of morphologic findings in reports of MLNS from Japan has convinced us that the structural alterations of fatal MLNS are indeed indistinguishable from those of IPN [52]. Furthermore, on the basis of published reports and our own experience with several cases of IPN, we agree with Tanaka that a clinical resemblance often exists between IPN and MCLS” [52].

Three years later, Landing and Larson published a retrospective study comparing 20 IPN autopsies with clinical findings of fatal MCLS patients in Hawaii and fatal MCLS cases in Japan. They reached two conclusions: first, that the “clinical and laboratory data presented for the 20 patients with IPN from the continental United States... appear[ed] sufficiently similar to, and in no way distinctly different from, those of patients with clinically verified MCLS”; and second, that “pathologically, neither the gross nor microscopic features, nor the patterns of distribution of lesions, of IPN appeared to warrant separation of IPN from fatal MCLS” [3].

4. The Kawasaki disease paradigm

As noted above, in the JRC’s original case definition, MCLS was described as an acute febrile illness with a

benign outcome [38]. Because the JRC designed the first case definition as a tool for epidemiological research rather than for clinical diagnosis, they emphasized specificity over sensitivity. The research definition would serve to differentiate this new syndrome from other diseases with similar physical findings, in particular SJS, scarlet fever, and acute rheumatic fever. The case definition required the presence of fever and at least three of four physical signs. These signs included conjunctival injection, exanthem, enanthem, and peripheral changes, but not cervical lymphadenopathy, reflecting Kawasaki's 1967 English language abstract title that a diagnosis was possible "with or without acute nonsuppurative cervical lymphadenitis" [1].

The JRC revised the case definition for the second national survey in 1972. While the committee did not change the criteria for diagnosis, it did list the coronary complications as an occasional finding (Table 3) [53]. Yamamoto explained that the committee again wanted the reporting of MCLS to remain specific and to exclude similar-appearing diseases [54,55]. The JRC feared that if cardiac complications were a diagnostic criterion or emphasized as a feature, physicians might mistakenly report cases of acute rheumatic fever as MCLS. Again, the JRC designed the case definition to detect patients with the clinical syndrome Kawasaki described in 1967, not to detect patients at risk for CAA. The second revision of the criteria, in 1974, added cervical lymphadenopathy as one of the six diagnostic criteria [56].

Meanwhile, in the United States, David Morens, an Epidemiological Information Service officer at the Centers for Disease Control (CDC), constructed an official CDC research case definition for MCLS based on the 1974 JRC criteria. He added the caveat that for a given case there could be no evidence of another disease with similar clinical features [57]. Morens had arrived at the CDC from the University of Hawaii in 1973. While a pediatric resident in Hawaii, he saw some of the first U.S. cases of MCLS under Melish's supervision, and he pursued his interest in KD at the CDC. At that time some senior CDC staff doubted that MCLS was a distinct syndrome, and in order to counter that view and to encourage reporting of

MCLS, Morens needed a specific case definition that physicians could use to report children who fit the definition of this illness. Prior to this time, the U.S. journals had referred to the new entity as MCLS, but Morens decided to call the entity *Kawasaki disease* rather than *Kawasaki syndrome*. Although Morens believed calling the illness a disease rather than a syndrome would give it more validity in the medical community, he did not intend for the case definition to be used as a diagnostic tool for therapeutic decisions [58]. Like the JRC, the CDC designed its definition to detect a distinct clinical syndrome and not patients at risk for CAA. But, contrary to Morens' intent, the CDC case definition was institutionalized in such venues as the *Redbook*, the official publication of the American Academy of Pediatrics Committee on Infectious Diseases [59], Feigin and Cherry's *Textbook of Pediatric Infectious Diseases* [60], and Cassidy and Petty's *Textbook of Pediatric Rheumatology* [61].

5. The challenge of history

Although successful in establishing KD as a distinct entity and saving many infants and children from lifelong coronary disease, the case definition produces two significant anomalies. First, strict reliance on the case definition leads to a delay in treatment of children who do not meet the criteria yet who are at risk for CAA [62–68]. Second, research has focused on those patients who fulfill the case definition and not those who develop CAA. If an etiological agent or mechanism makes CAA more likely in children with atypical KD, strict reliance on the case definition may impede its discovery.

The increasing number of atypical cases led the JRC to revise its case definition in 1984 to include patients with fever and only three of five physical signs, if coronary artery changes are present [69,70]. However, the CDC case definition remained unchanged, and the American Heart Association guidelines rely on the CDC diagnostic criteria but allow a diagnosis of KD when fewer than four principal physical signs accompany CAA [71,72]. The *Redbook* guidelines also allow for the diagnosis of KD in children with fewer than four criteria if CAA are present [73]. Thus, after 30 years, the diagnostic criteria are largely based on the same clinical signs as those of the second revision of the JRC case definition [56].

Because the criteria create an anomaly (excluding some patients with coronary artery abnormalities only uncovered later by echocardiogram or autopsy), revisions of the criteria have moved in the direction of including atypical patients with demonstrated CAA. These revisions are an attempt to preserve the paradigm by including the atypical presentation as a *forme fruste* of KD—in other words, atypical cases that have the same etiology as typical KD. As with all syndromes, however, KD has no known etiology and therefore the existence of a *forme fruste* is moot. In fact,

Table 3
Japan MCLS Research Committee (JRC) Criteria, 1972

Indispensable symptoms (number 1, plus three of 2 to 5)
1. Fever continuing 5 or more days, not responding to antibiotics
2. Congestion of bilateral ocular conjunctivae
3. Changes of peripheral extremities
a. Indurative edema (initial stage)
b. Erythema of palms and soles (initial stage)
c. Membranous desquamation from fingertips (convalescent stage)
4. Changes in the lips and mouth
a. Dryness, redness, and fissuring of lips
b. Swelling of tongue papillae (strawberry-like)
c. Diffuse reddening of the oral and pharyngeal mucosa
5. Polymorphous exanthem of body trunk without vesicles or crusts

many researchers recognize the fallacy of this approach and exclude atypical patients from their research into the etiology of KD. These revisions do, however, create a paradox whereby atypical cases receive delayed treatment because diagnosis is only made after CAA is present, thus negating the goal of CAA prevention [74]. An effort is underway to revise the KD case definition. There is a consensus that a new clinical definition, one that includes laboratory findings and deemphasizes some clinical signs, such as cervical lymphadenopathy, is necessary. Drafts of that definition are now under review by the American Heart Association.

Although the main aim of diagnosis and treatment is to prevent the development of CAA, it has taken almost 40 years for the focus to return to the pediatric vasculitis first identified by Roberts and Fetterman in 1963 [22]. The majority of KD research continues to focus on the as yet unidentified etiological agent. Although this effort certainly is important, much less focus has been extended to the pathophysiology of the vasculitis itself. Part of the reason for this delay must be attributed to the extraordinary power of Kawasaki's clinical case definition in published first in 1967. Like all useful paradigms, the KD case definition was successful in identifying and preventing heart disease in a great number of children, despite the fact that Kawasaki had designed it for a benign syndrome with no cardiac sequelae. Kawasaki continues to maintain that KD and IPN are different disorders [39]. Whether Kawasaki is correct or not, one wonders what the result would have been had his viewpoint been incorporated into the general lexicon of this syndrome.

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