Kawasaki disease: Etiology, pathogenesis, and treatment

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Kawasaki disease is an acute febrile illness of childhood and is the primary cause of acquired heart disease in children in the United States and Japan. Initially described by Kawasaki in 1967,[1] the syndrome was thought to be a benign, self-limited febrile illness. It is now known to be a systemic vasculitis occurring predominantly in small and medium-sized muscular arteries, especially the coronary arteries. Cardiac sequelae account for most of the morbidity and mortality of the disease, and treatment is based on prevention of aneurysm formation.

EPIDEMIOLOGY

Eighty percent of cases of Kawasaki disease occur in children younger than 5 years of age. The peak incidence is in children 2 years of age and younger, with boys affected 1.5 times as often as girls. Recurrences occur in 2% to 4% of cases,[2,3] and familial incidence is approximately 2%.[4]

Although all racial groups are represented, children of Asian ancestry continue to predominate, with the incidence in the Japanese being highest at approximately 50 to 200 per 100,000 children younger than 5 years of age.[3,5] In the United Sates, reports of incidence range from six to 15 per 100,000 children younger than 5 years of age,[6] with Asian Americans being proportionately overrepresented and white Americans being proportionately underrepresented. New cases occur throughout the year in North America, with larger numbers occurring in late winter to early spring.

The occurrence in siblings is rare. In a nationwide study in Japan, the overall second-case rate for siblings was 2.1% compared with an overall incidence of approximately 0.19% in the general population of children 0 to 4 years of age.[4] More than half of the second cases developed 10 days or fewer after the first case occurred.

CLINICAL FEATURES

The principal diagnostic criteria include: 1) fever lasting more than 5 days; 2) conjunctival injection; 3) oropharyngeal changes including erythema, swelling and fissuring of the lips, diffuse erythema of the oropharynx or strawberry tongue; 4) peripheral extremity changes including erythema of the palms and soles, induration of the hands and feet, desquamation of the skin of the hands and feet, or Beau's lines (transverse grooves in the nails); 5) polymorphous rash; 6) cervical lymphadenopathy, usually a single node >1.5 cm. Five of the six criteria, with fever being an absolute, must be present for diagnosis. "Atypical" cases may be diagnosed with fewer criteria when coronary artery aneurysms are noted by echocardiography or angiography. There are a number of associated manifestations that may aid in the diagnosis of Kawasaki disease. Among these are: irritability, sterile pyuria, meatitus, perineal erythema and desquamation, arthralgias, arthritis, abdominal pain, diarrhea, hepatitis, obstructive jaundice, hydrops of the gallbladder, pulmonary infiltrates, pleural effusions, uveitis, sensorineural hearing loss, and cardiovascular manifestations.[7,8]

CARDIAC DISEASE

Cardiac abnormalities manifested during the acute stage include pericardial effusions in approximately 30% of cases. Myocarditis is also common in the acute phase and is manifested by tachycardia and gallop rhythm. Congestive heart failure and atrial and ventricular arrhythmias can occur. Electrocardiogram findings include decreased R-wave voltage, ST segment depression, and T-wave flattening or inversion. Slowed conduction can also occur with PR or QT prolongation.[9] Mitral regurgitation may be present in approximately 30% of patients, although it is usually mild.[10] Aortic valve involvement has also been described.[11]

Coronary artery lesions are responsible for most of the morbidity and mortality of the disease. They developed in approximately 15% to 25% of patients prior to the widespread use of intravenous immune globulin (IVIG), but now occur in less than 10%. Aneurysms usually appear from 1 to 4 weeks after onset of fever, and it is rare to detect new lesions after 6 weeks. Aneurysms are most easily detected by transthoracic two-dimensional echocardiography. Aneurysms are described as small (<4 mm), medium (4 to 8 mm), or giant (>8 mm), and are more commonly proximal than distal. Ectasia of the vessels (vessel size larg-

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er than in age-matched controls) is also a common finding. Small and medium-sized aneurysms generally regress radiographically within 5 years of follow-up[12]; however, these vessels most likely remain abnormal, because response to pharmacologic dilation may remain impaired.[13] Pathologically regressed aneurysms may reveal abnormal intimal proliferation[14] and in fact may also be associated with narrowed lumens and calcified arterial walls, despite the fact that these changes may not be apparent on arteriography.[15] Therapy with IVIG has decreased the incidence of giant aneurysms,[12] which rarely regress and frequently develop complicating thromboses, stenosis, or total occlusion. Myocardial infarction may result; when it occurs, it is most likely to be in the first year, with 40% occurring in the first 3 months of illness.[16] There are, however, reports of young adults suffering myocardial infarctions more than a decade after their initial disease and others with coronary artery aneurysms who were not known to have had Kawasaki disease as children.

■ ETIOLOGY

Despite years of intensive investigation, the etiologic agent of Kawasaki disease remains elusive. Many of the clinical features suggest an infectious etiology, including the fever, exanthem, conjunctival injection, cervical adenopathy and self-limited nature of the illness. In addition, the epidemiologic features including well-defined epidemics with winter-spring predominance and a geographic clustering of cases suggest an infectious etiology.

The peak incidence in early childhood and the virtual absence of Kawasaki disease in adults suggests the causative agent(s) is a ubiquitous microbe that causes an asymptomatic infection in most individuals with acquired immunity by adulthood. The rarity of illness in infants less than 3 months of age suggests passive protection via maternal antibody. The search for an etiologic agent could cover an infectious disease textbook. Because most ubiquitous microbes enter the host via the respiratory or gastrointestinal tracts, one or both of these portals of entry would be likely for the putative agent(s).

Bacteria?

Kawasaki disease shares features with a number of well-characterized bacterial or rickettsial infections, including:

- Staphylococcal or streptococcal toxic shock syndrome
- Rheumatic fever
- Scarlet fever
- Staphylococcal "scalded skin" syndrome
- Rocky Mountain spotted fever
- Leptospirosis

However, in the more than 30 years since the initial report of this disease, none of these can claim responsibility. In an interesting report from Shibata in 1999,[17] nested PCR was used to amplify bacterial ribosomal DNA from PBL obtained from patients with Kawasaki disease. Analysis of a sequence obtained in 3/20 patients revealed a new *Corynebacterium* species. With the exception of *C diphtheriae*, corynebacteria have been considered unimportant as the cause of human diseases. Coryneform bacteria are members of the normal flora of skin and cutaneous membranes; thus, corynebacteria would have been easily missed in the bacterial culture of the nasopharynx from patients with Kawasaki disease. However, increasing evidence shows pathogenic roles for several corynebacteria, and it will be interesting to see future studies.

Virus?

Using techniques of viral isolation and/or serologic confirmation, the following viruses have been incriminated as possible etiologic agents of Kawasaki disease:

- Measles virus
- Epstein-Barr virus
- Adenovirus
- Parainfluenza virus
- Rotavirus
- Influenza virus
- Herpesvirus 6 (HHV6)
- Parvovirus

The wide variety of agents encountered and the failure to demonstrate any unique serologic relationship suggest that these viruses are likely to be either incidental or to play some sort of a "helper" role in the pathogenesis of KD. Furthermore, Chua[18] used PCR to determine whether Kawasaki could be the result of infection by parvovirus B19, human herpesvirus 8, TT virus, GB virus C/hepatitis G virus, or *Chlamydia pneumoniae*. The data do not support an etiologic association between Kawasaki disease and infection with any of these agents.

Retroviruses held a place on the front page of the news as a possible etiologic agent for a number of years. In 1986, DNA polymerase activity was reported from cultured peripheral blood mononuclear cells (PBMC) in patients by 2 independent groups. Burns[19] reported that retrovirus-associated reverse transcriptase (RT) activity was found in culture supernatants of PBMC from 14 patients but not in febrile controls. Shulman and Rowley[20] demonstrated RT activity in 8/18 patients but in only 1/18 controls using co-cultivated PBMC/lymphoblastoid cell supernatants. Melish[21] was unable to demonstrate significant RT activity or other evidence of involvement of retrovirus in the etiology of Kawasaki disease. It was later considered that these initial findings were typical of DNA-dependent DNA polymerase rather than viral RT.[22]

Epstein-Barr virus and Kawasaki disease. EBV generally infects asymptomatically in the vast majority. However, in some instances it causes or relates to the development of a wide spectrum of diseases such as infectious mononucleosis, lymphoproliferative disorder (which occurs in immunologically compromised individuals), hemophagocytic syndrome, chronic active EBV, Burkett's lymphoma and nasopharyngeal carcinoma. Infection occurring in conjunction with an imbalance or deficiency in the normal immune response is considered to increase the risk of development of a range of EBV-associated disorders, as listed above. Kikuta[23] reported detection of EBV genome in 3 cardiac tissue samples and one aortic tissue sample examined by PCR obtained from 3 patients with chronic, active EBV infection associated with Kawasaki-like coronary artery aneurysms. However, none of these patients

had clinical hallmarks of Kawasaki disease. However, Culora[24] was unable to detect EBV-encoded RNA by in situ hybridization in postmortem sections of a coronary artery and myocardium of a patient suspected of having Kawasaki disease. In addition, Marchette[25] found no serologic evidence of EBV infection in Kawasaki patients. For the time being, EBV may be taken off the "most wanted list."

Chlamydia has also taken a lead in the popularity race over the years. C *pneumoniae* is a common respiratory pathogen and is a plausible infectious trigger for Kawasaki disease because it has been linked to endocarditis and myocarditis in children and to an increased risk of atherosclerosis and heart attacks in adults. There is intriguing molecular mimicry between the outer membrane protein of chlamydiae and cardiac alpha myosin, thus providing a mechanism by which *Chlamydia* infection might trigger an immune response to the myocardium. Serologic studies indicate that C *pneumoniae* infections occur most commonly among children 5 to 15 years old. However, serologic studies may underestimate the prevalence of C *pneumoniae* in young children because infected children do not always mount an antibody response. The majority of infections in children are mild or asymptomatic and rarely present as pneumonia. In a study by Normann,[26] C *pneumoniae* was detected by immunohistochemistry in heart tissue specimens from 2 children who died of Kawasaki disease. (Note, however, that this association was based on a small sample size and control tissues from children without Kawasaki disease were not examined.) However, Schrag et al[27] analyzed blood, urine, and pharyngeal specimens from Kawasaki patients for evidence of recent C *pneumoniae* infection by culture, PCR, and serology and found no evidence of current C *pneumoniae* infection in Kawasaki patients. Furthermore, Strigl et al[28] found no difference in the prevalence of anti-chlamydial IgG, IgM, and IgA between Kawasaki patients and controls.

An association with mycobacterial antigens has been suggested because of the inflammatory change that occurs at the site of a previous bacillus Calmette-Guérin (BCG) immunization in children with Kawasaki disease[29,30] and the temporarily positive response to mycobacterial HSP antigens in children with acute Kawasaki disease.[31,32] Whether these responses represent a specific reaction to mycobacterial antigens, or represent a more general response to bacterial or other heat-shock proteins that are cross-reactive, is not clear.

Noninfectious causes that must be considered include:

- Infantile polyarteritis nodosa
- Mercury toxicity (acrodynia)
- Stevens-Johnson syndrome
- Erythema multiforme
- Adverse drug reactions
- Systemic juvenile rheumatoid arthritis
- Association with rug shampoo

In the 1980s, dust mites and rug shampoo were high on the list of possible etiologic agents. In a report in *Lancet* in 1982, Patriarca[33] indicated that the application of rug shampoo during the month before onset of disease was associated with the occurrence of Kawasaki disease. Daniels[34] evaluated the published case-control studies and found 2 studies with significant associations and 3 studies with no association. Rickettsia-like particles were reportedly found in the digestive tracts of house dust mites obtained from the homes of patients.[35] While there was a flurry of publications regarding dust mites and rickettsia-like particles in the 1980s, current literature is devoid of its mention. With the passage of time, the possible association of rug shampoo and Kawasaki disease has faded from popularity.

Superantigen theory

Features of Kawasaki disease are similar to those found in certain illnesses that are caused by toxin-producing bacteria, such as toxic shock syndrome and scarlet fever. Staphylococcal enterotoxins and streptococcal exotoxins are prototypic superantigens that stimulate large populations of T cells in a class II MHC-dependent, yet unrestricted manner. These toxins bind directly to conserved amino acid residues outside of the antigen-binding groove on class II MHC molecules and selectively stimulate T cells expressing particular β-chain variable gene segments.

Other variable elements (Dβ, Jβ, Vα, Jα) of the TCR contribute much less to the recognition of these superantigens. All T cells possessing a specific sequence on the TCR are activated by the MHC-superantigen complex, and this may represent as many as 20% of circulating lymphocytes. The result is an unusually large amount of cytokines from activated T cells, hence the name "superantigen." One hallmark of T-cell activation caused by a toxin with superantigenic activity is an increase in the number of T cells expressing a specific TCR Vβ region. (In contrast, conventional peptide antigens usually require all 5 variable elements for T-cell recognition and therefore stimulate only a low frequency of T cells).

A report in 1992 first described selective expansion of Vβ 2+ T cells and to a lesser extent Vβ 8.1+ T cells in patients with acute Kawasaki disease[36] similar to that seen in patients with toxic shock syndrome. During the convalescent phase, the overrepresentation of the Vβ2+ and Vβ8.1+ T cells returned to normal, indicating that the increase occurs after the onset of Kawasaki disease and is not a marker of susceptibility. (Note: TCR Vβ expression was assessed after in vitro cultivation of T cells in the presence of anti-CD3 antibodies.) Since the release of this report, a flurry of reports, either supporting or denouncing this claim, have surfaced. The jury is still out deliberating whether the superantigen theory is still plausible. While we are waiting for the verdict, I will present evidence for both sides of the argument.

Positive evidence of superantigens

- **Abe 1993**[37]—Confirmed that the increase in Vβ2-bearing T cells occurred primarily in the CD4 cell subset. Sequence analysis of TCR β chain genes of Vβ2 and Vβ8.1 expressing T cells from acute KD patients showed extensive junctional region diversity, supporting the concept of a polyclonal expansion.
- **Leung 1993**[38]—Bacteria were cultured from throat, rectum and groin of 16 patients with untreated

acute KD and 15 controls. Bacteria-producing toxins were isolated from 13/16 KD patients but only 1/15 controls. TSST-secreting *Staphylococcus aureus* was isolated from 11/13 toxin-positive cultures, and streptococcal pyrogenic exotoxins (SPE) B and C were found in the other 2.

- **Curtis 1995**[39]—using monoclonal antibodies to TCR Vβ2, 5, 8, 12, 19, found the mean percentage of Vβ2 expressing T cells in KD patients was increased. Did **not** find a selective increase in Vβ8 bearing T cells (as did Abe[36]).
- **Leung 1995**[40]—KD patients demonstrated elevated levels of TCR Vβ2+ and to a lesser extent Vβ8.1+ T cells in comparison to cells from normal donors and control patients with other febrile illnesses. During convalescence, the proportion of Vβ2+ and Vβ8.1+ T cells returned to normal levels.
- **Yamashiro 1996**[41]—the occurrence of Vβ2+T cells was found to be selectively increased in the small intestinal mucosa of 12 patients with acute KD compared to controls. No significant difference in the occurrence of Vβ+ T cells was noted in the jejunum compared to controls. Did NOT find TCR Vβ significant expansion of T cells in the peripheral blood compared to controls.
- **Masuda 1998**[42]—investigated peripheral T-cell response to superantigens by measuring proliferation and IL-2 production to determine whether there is T-cell anergy induced by superantigens in KD patients. T cells from patients in acute or convalescent stage showed significantly lower proliferation and IL-2 production than did T cells from healthy control subjects following stimulation by SPE-C, but not SPE-A or TSST-1. The T-cell response to SPE-C normalized within 1 year. These results may indicate that the transient low T-cell response to SPE-C in patients may have been related to superantigen-induced anergy or disappearance of SPE-C responding cells from the circulation. They did not examine evidence of invasion of SPE-C or the presence of Strep-producing SPE-C in patients and thus did not confirm a direct role for SPE-C in the etiology.
- **Yoshioka 1999**[43]—the mean percentage of Vβ2- or Vβ6.5-bearing T cells in PBMC in the acute phase was significantly higher than that of patients in the convalescent phase of KD or in healthy donors. This expansion was polyclonal because DNA sequences in the complementarity-determining region 3 of Vβ2 and Vβ6.5+ cDNA clones were all different from each other.

Negative evidence of superantigens

- Group A β-hemolytic Strep has not been consistently isolated from patients; ASO titer is not raised; lack of response to antibiotics.
- **Sakaguchi 1993**[44] found no difference in percentage of Vβ2+ or Vβ8.1+ T cells among patients with acute, convalescent KD, age-matched controls and adults.
- **Pietra 1994**[45]—Using flow cytometry, reported no expansion of any Vβ family in acute KD.
- **Marchette 1995**[46]—Found no evidence of etiological association between exposure to TSST-1 and development of KD.
- **Tristani-Firouzi 1995**[47]—selective expansion of Vβ2 and Vβ8.1 families was not observed.
- **Abe 1995**[48]—Could not confirm that TSST-1 secreting *S aureus* is specifically associated with Kawasaki disease nor that the superantigen produced by the staphylococcal isolates is related to the change of TCR repertoire. They postulated that an unknown etiologic agent stimulates Vβ2 positive T cells or that the Vβ2 expansion in PBMC may be caused by an unknown immunopathological process.
- **Nishiyori 1995**[49]—No expansion of Vβ2- and Vβ8.1-expressing T cells. No increase in anti-TSST-1 titer.
- **Todome 1995**[50]—There were no noticeable differences between *S aureus* strains from KD patients and control children in the production of staphylococcal exotoxins A-E, coagulase serotype, hemolysis of sheep erythrocytes, and tryptophan auxotrophy. The pathological or etiological role of a new TSST-1 secreting *S aureus* clone in patients with KD was not confirmed. Group A Strep could not be isolated from either KD patients or controls.
- **Terai 1995**[51]—Culture supernatants of bacterial isolates from patients did not support involvement of toxin-producing staphylococci in KD.
- **Deresiewicz 1996**[52] found no evidence of an *S aureus* strain or TSST-1 sequence uniquely associated with KD.
- **Morita 1997**[53] examined serum antibody responses to superantigens in paired acute/convalescent sera from KD patients and found a very low frequency of detection of anti-superantigen antibodies and no marked IgG seroconversion.
- **Choi 1997**[54] found clonal expansion of TCR Vβs in some patients, suggesting that the antigen that induced the expansion of T cells may have belonged to the conventional antigens rather than to the superantigens. (These clonal expansions were found mainly in the CD8+ T cells.)
- **Mancia 1998**[55]—No abnormal usage of any TCR Vβ family was found, neither acutely nor during convalescence compared to a group of healthy children.
- **Nomura 1998**[56] examined 25 Vβ families. Selective expansion of the Vβ family in KD was not observed. The pattern of increased Vβs did not show the specific pattern that indicates a particular superantigen.

The jury is still out. After reviewing the gamut of infectious (and non-infectious) etiologies, the etiologic agent is still elusive. The longer that a single infectious agent cannot be identified as the cause of Kawasaki disease, the more the possibility must be considered that multiple agents, each of which can lead to a common pathway, may result in this clinical syndrome. It is possible that the disease is triggered by infection (early acute

stage) and thereafter rheumatic manifestations (immunologically mediated reaction to the initiating infection) follow. Alternatively, the agent may have already been cleared from the sampled compartment at the time of specimen collection.

The close temporal association of KD with acute infection with multiple common agents suggests 3 possibilities: the association may be entirely coincidental; Kawasaki disease represents a cascade of host responses that can be triggered by infection with more than one agent; or common infectious agents infecting acutely ill Kawasaki patients may be acting in a "helper" role to activate or enhance pathogenic expression of the real causative agent. While the stereotyped nature of Kawasaki disease makes the multiple pathogenesis hypothesis unlikely, no primary agent has been identified despite extensive search. Another plausible explanation for the largely negative results may be that a previously unidentified microbial agent causes Kawasaki disease.

Immune abnormalities

Laboratory findings in acute Kawasaki disease reflect the marked degree of systemic inflammation. Early in the course of disease, laboratory evaluation reveals a leukocytosis with a left shift and elevation of acute phase reactants, as measured by the erythrocyte sedimentation rate, serum α1-antitrypsin and quantitative C-reactive protein measurements. A global lymphocytosis follows with a predominance of B cells.[57] Despite evidence of a polyclonal B-cell activation, the antibody repertoire in these patients is poorly defined. Sera from patients with acute KD do not contain the usual antibodies frequently associated with other collagen vascular diseases—no RF, ANA, anti-DNA, or ANCA. In the subacute stage of the disease, platelet count increases and frequently reaches 1,000,000 per microliter or greater by the 3rd week of illness.

B cells are not alone in this state of activation. There is evidence of T-cell activation as well, with increased numbers of CD4+ and CD8+ cells bearing MHC class II antigens[57] and increased levels of soluble interleukin-2 receptors.[58-60]

Striking immunologic perturbations occur in the acute stage of KD. Patients demonstrate cutaneous anergy with delayed-type hypersensitivity reaction on skin testing, supporting the notion of a global dysfunction of circulating T cells.[57]

There is evidence of cytokine cascade activation and endothelial cell activation. Circulating levels of a number of cytokines—tumor necrosis factor-α (TNF-α),[58,60-66] interferon-γ (IFN-γ),[58,63,67,68] interleukin 1 (IL-1),[69] IL-6,[60,64,65,70,71] and IL-8[60,65,72]—have been reported. Peripheral blood mononuclear cells (PMC) from patients with acute, but not convalescent KD spontaneously produce high levels of IL-1[73] and TNF-α.[74,75] These cytokines elicit an overlapping set of proinflammatory and prothrombotic responses in endothelial cells. The acute phase of KD is associated with the appearance of circulating antibodies that are cytotoxic against vascular endothelial cells pre-stimulated with IL-1, TNF-α[76] or IFN-γ,[77] but to a lesser extent or not at all against unstimulated endothelial cells. Successful treatment of KD patients with IVIG plus ASA is associated with a reduction in their cytokine production and endothelial cell activation.[78] In contrast, patients treated with aspirin alone have prolonged T- and B-cell activation.

In a series of reports, anti-endothelial antibodies have been demonstrated in the sera of acute KD patients.[73,76,77,79-81] These antibodies lysed human umbilical vein endothelial (HUVE) and human saphenous vein endothelial (HSVE) cells pretreated with cytokines, including TNF or interferon-gamma. One can postulate that Kawasaki disease is associated with cytokine-mediated endothelial cell activation, possibly including the intimal surfaces and the vasa vasorum of medium-sized arteries. This activation may be associated with the expression of new endothelial cell antigens and functional endothelial cell changes and culminates in an immune response directed against the abnormal stimulated vascular endothelial cell with influx of inflammatory cells into the media with consequent weakening of the vessel wall and predisposition to aneurysm formation.

Adherence of leukocytes to endothelial cells is a key event in the sequence of an inflammatory response. As an initial event during inflammation, leukocytes in the blood stream roll along endothelial cells with loose contact mediated by E-selectin, P-selectin, and L-selectin. In the second phase of inflammation, activation of leukocyte integrins occurs with expression of immunoglobulin-like adhesion proteins on endothelial cells, including intercellular adhesion molecules (ICAM) and vascular cell adhesion molecule (VCAM). Leukocyte traffic across the vascular endothelium is dependent on interaction between leukocytes and endothelial cells mediated by a variety of cell adhesion molecules. Elevated levels of soluble forms of these molecules have been found in conditions associated with endothelial cell activation and inflammation and are thought to be formed by cleavage of the membrane-bound form and release into the circulation of the extracellular domain. Levels of circulating ICAM are also increased in the acute phase of KD.[82-85] ICAM-1 and E-selectin expression on endothelial cells has also been detected in biopsy samples of skin from patients with acute KD.[73]

■ PATHOLOGY

The pathology of acute KD reveals a panvasculitis of the small and medium-sized muscular arteries with endothelial edema, necrosis, desquamation, and leukocyte infiltration of the arterial wall. Inflammatory cells are initially neutrophils but rapidly change to mononuclear cells (paralleling what is seen in the periphery). Infiltration of macrophages and activated T cells has been observed in the vascular lesions of KD.[85] The inflammatory process frequently involves the entire vascular wall. Edema and necrosis cause the wall to lose its structural integrity, leading to formation of aneurysms. One to two months later, the inflammatory cells are less apparent, and fibrous connective tissue begins to form within the vessel wall. The intima proliferates and becomes thickened. Eventually the wall may become stenotic or occluded by either stenosis or thrombosis.

The IgA plasma cell story

A new twist to the Kawasaki story was launched in 1997 when Rowley et al[86] reported the presence of IgA plasma cells in the vascular wall of patients with KD. This was a surprising finding as blood vessels in other disease states have not been found to be infiltrated by immunoglobulin-producing B cells, or, even more surprising, IgA-producing plasma cells. These IgA plasma cells were noted primarily in the adventitial layer in an artery with mild vasculitis but in all 3 layers of the coronary arteries when panarteritis was present. They postulated that the inflammatory reaction in the vascular wall in Kawasaki disease is initiated in the adventitial layer, around the vasa vasorum, and ultimately progresses to involve all 3 layers of the vascular wall in more severely affected arteries, indicating that the coronary artery lumen endothelial cell is not the primary site of vessel damage. It was speculated that IgA-producing cells migrate to the vascular tissue and myocardium in KD by the following pathway. An etiologic agent with a gastrointestinal or respiratory portal of entry is processed in the gut-associated lymphoreticular tissue or in the bronchus-associated lymphoid tissue. B cells undergo switching to IgA-precursors, leave the gut-associated lymphoreticular tissue or bronchus-associated lymphoid tissues, enter the general circulation, and migrate to the vascular wall and myocardium.

In a larger series of patients, plasma cell infiltration was prominent in the proximal respiratory tract, especially the submucosal glands of the trachea and large bronchi (with relative sparing of the distal lungs) as well as pancreatic ducts and kidneys.[87] The infiltration by IgA plasma cells was independent of the vasculitis in the respective organ. These data suggest a respiratory portal of entry of the KD etiologic agent with subsequent spread through the blood stream.

In a recent study, Rowley[88] examined the clonality of the IgA response by sequencing the CDR3 region of the α genes isolated from the vascular tissue of fatal acute KD patients. The IgA produced in acute KD is oligoclonal, consistent with an antigen-driven immune response.

Animal models of Kawasaki disease

A number of animal models have been described:

- *Candida albicans* extracts injected into mice induce systemic angiitis.[89]
- An experimental allergic angiitis in rabbits with horse serum injection leading to serum sickness hypersensitivity and coronary arteritis has been used in combination with a dietary model of atherosclerosis. A relationship was identified between the migration of smooth muscle cells into thickened intima and premature atherosclerosis.[90,91]
- Juvenile polyarteritis syndrome in beagles occurs spontaneously.[92] The treatment of these dogs with prednisone resulted in a rapid clinical improvement accompanied by a decrease of IL-6 activity.
- Lehman et al developed a murine model of coronary arteritis with a single intraperitoneal injection of *Lactobacillus casei* cell wall fragment.[93] Histopathologic study revealed mononuclear cells in the adventitia of the coronary arteries, followed by focal asymmetrical invasion of the vessel wall and later circumferential lesions with a marked proliferation of the intima/media, narrowing/obstruction of the lumen, and proliferation of adventitial fibrous tissue. Dense fibrous tissue around the coronary arteries, luminal narrowing from intimal proliferation, and recanalization after thrombosis followed. This model has been used to investigate various modalities to suppress coronary arteritis, which may provide clues to the pathogenesis of the early inflammatory response.[94]

The issue with all these models is how applicable they are to KD. Data must be accumulated to show how similar they are to KD to assess whether information can be extrapolated to KD. A true model of disease would involve transmission of an (infectious) agent from a child with KD to a susceptible host with duplication of the clinical and laboratory findings in the animal model. Attempts by us as well as others to transmit an agent from KD specimens to mice, rabbits, guinea pigs and macaques have been unsuccessful. At this meeting we will report our attempt to transmit Kawasaki disease to young chimpanzees.

■ TREATMENT AND LONG-TERM FOLLOW-UP

Treatment in the acute phase of the disease is aimed at limiting inflammation. Treatment with IVIG in various regimens has been shown to significantly reduce myocardial inflammation and the incidence of coronary artery aneurysm formation, as well as lead to a rapid defervescence and more rapid normalization of acute phase reactants.[95-97] In the United States, the standard of care is 2 g/kg IVIG as a single infusion. The efficacy of IVIG has been studied only during the first 10 days of illness. No controlled studies have been conduced regarding treatment later than the 10th day of illness, although therapy is recommended for such children with continued fever and features of acute inflammation, as persistent or recurrent fever is a major risk factor for the development of coronary abnormalities in patients with KD.

Aspirin is administered for both its anti-inflammatory and antithrombotic effects. It is given concurrently with the IVIG at a dosage of 80 to 100 mg/kg/d. The pharmacokinetic properties of aspirin are altered in children with acute KD, with decreased absorption and increased clearance of drug.[98] Therefore, most children with acute KD do not achieve therapeutic serum salicylate concentrations (20-30 mg/dL) despite the administration of high doses of aspirin. Once the patient has been afebrile for 48 to 72 hours, the dose can be lowered to 3 to 5 mg/kg/d, which is sufficient for the antiplatelet effect. This dose is continued until the platelet count and other indicators of inflammation (sedimentation rate) return to normal (about 8 weeks of illness). Although long-term, low-dose aspirin is recommended for any child in whom persistent coronary artery abnormalities have been detected, the efficacy of this approach for the prevention of coronary thrombosis has not been documented by controlled studies.

Treatment with high-dose IVIG and aspirin has be-

come the standard of care in the United States. However, even when high-dose IVIG is administered within the first 10 days of illness, approximately 5% of children with KD develop at least transient coronary artery dilation and 1% develop giant aneurysms.[99] Approximately 10% of children treated with IVIG have persistent or recurrent fever despite IVIG treatment.[97] If the fever persists, a second dose of IVIG at 1 g/kg may result in defervescence, although it is unknown whether retreatment prevents the development of coronary artery lesions.[100,101]

A subgroup of patients with Kawasaki disease is resistant to IVIG therapy; these patients are at greatest risk of development of coronary artery aneurysms and long-term sequelae of the disease. No effective treatment for these patients with refractory disease has been established. Although corticosteroids are the treatment of choice in other forms of vasculitis, their use in Kawasaki disease has been controversial. Reluctance to use steroids in acute KD derived from an early study by Kato et al,[102] demonstrating an extraordinarily high incidence of coronary artery aneurysms (11 of 17 patients) in a group that received oral prednisolone at a dose of 2 to 3 mg/kg/d for at least 2 weeks, followed by 1.5 mg/kg/d for an additional 2 weeks. What is often overlooked is that in the same study a smaller group of 7 patients received prednisolone plus aspirin, and none developed aneurysms. Following this report, many physicians were reluctant to administer steroids to children with KD. In a randomized trial in 100 children treated with intravenous prednisolone (followed by an oral taper) versus low-dose IVIG (300 mg/kg/d for 3 days), Nonaka et al[103] reported shorter fever duration in the steroid-treated group, but no significant difference in the prevalence of coronary aneurysms. Other studies have suggested that both oral[104] and intravenous[105] steroids may have a beneficial effect on coronary outcome. Wright et al[106] described preliminary results showing that some patients with IVIG-resistant Kawasaki disease can be treated safely with intravenous pulse steroid therapy. Shinohara reported that treatment with prednisolone was associated with a significantly shorter duration of fever after institution of treatment, as well as with a lower prevalence of coronary artery aneurysms.[107] In view of intriguing initial data suggesting that steroid therapy may be beneficial and that its adverse effects with short-term use are low, the efficacy of steroid administration in the treatment of KD should be assessed with randomized controlled studies.

Additional therapeutic options have been suggested; however, no formal consensus as to efficacy has been achieved. In response to reports of elevated TNF-α and soluble TNF receptor levels in acute Kawasaki disease,[44,61,66] pentoxifylline (thought to block TNF-α production) has been tried in combination with IVIG.[108] This preliminary study, which reported efficacy in reducing the incidence of coronary artery lesions when administered early in the course of Kawasaki disease, awaits confirmation by other investigators. A logical extension to the concept of reducing the effect of TNF-α is the treatment with one of the newer anti-TNF agents, such as etanercept or infliximab. To date, there has been no controlled study evaluating the efficacy of this type of treatment in Kawasaki disease.

The duration, frequency, and best imaging methods for the long-term follow-up are still a matter of debate. Of greatest concern are those children with initial coronary artery aneurysms, because thrombosis or segmental stenosis may occur in the chronic phase of the disease. The American Heart Association has recommended guidelines for long-term follow-up.[99] Children with multiple aneurysms, giant aneurysms, or known coronary artery obstruction require close follow-up and possible long-term anticoagulation therapy. Stress testing in the adolescent years is important, especially in those patients with a history of coronary artery involvement, because abnormalities may require limitations in physical activity and may indicate the need for angiography to assess the degree of coronary artery stenosis or obstruction.

Severe coronary artery complications of Kawasaki disease have been treated by a variety of coronary artery bypass procedures.[109-111] There is a small population of patients in whom revascularization procedures are not successful or not possible because of the extent of their disease. This has led to consideration of cardiac transplantation in these patients.[112] The most common indication for transplantation is ischemic left ventricular dysfunction, occurring usually later than 1 year after onset of Kawasaki disease.

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