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Is Kawasaki Disease an Infectious Disorder?

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Abstract

Although the etiology of Kawasaki Disease (KD) is largely unknown, a large body of clinical, epidemiologic, immunologic, pathologic and ultrastructural evidence suggests that an infectious agent triggers a cascade that causes the illness. This elusive infectious agent, however, remains unidentified at present. Increasingly sensitive molecular methods for identifying microbial nucleic acids and proteins in tissue samples continue to rapidly emerge, and these methods should be utilized in studies on KD etiology as they become available. Identifying the etiology of this enigmatic diseases remains the single most important research goal in the field, and accomplishing this goal is the best means to improve diagnosis, treatment, and prevention of this potentially fatal childhood disease.

Keywords

Acquired immune response; Cytotoxic T lymphocytes; IgA; Interferon; Oligoclonal antibodies

Kawasaki disease (KD) is the most common medium vessel vasculitis in children. Etiology of this disease is a major pediatric mystery. Among the human vasculitides, KD has features that appear most supportive of an infectious cause. This includes clinical and epidemiologic, pathologic, immunologic, ultrastructural, and transcriptional data. Based upon numerous studies over several decades, however, no known infectious agent causes KD.¹

Clinical features

The abrupt onset of high fever in previously healthy children is characteristic of KD and supports acute infection. The clinical findings of conjunctival injection, oral and pharyngeal erythema, cervical adenopathy, and rash are very similar to those observed in other pediatric infections acquired by the respiratory route. The occurrence of self-limited aseptic meningitis, hepatitis, and arthritis in a subset of KD patients supports systemic infection, and the failure of KD patients to respond to antibiotic therapy argues against a bacterial pathogen as an etiologic agent. The self-limited clinical findings and generally non-recurring nature of the febrile illness are highly suggestive of an infection, and not of an autoimmune process.

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Conflicts of interest: none

Epidemiologic features

KD usually affects very young children, mostly those < 5 years, with peak incidence at 9-11 months of age.^{2,3} This is a typical peak age for common childhood infections, because it corresponds with the timing of a significant decrease in passive maternal antibodies. The theory that maternal antibody is protective against it, is supported by rarity of KD before 3 months of age. In contrast, autoimmune diseases are quite rare in infants. KD has been associated with epidemics and clusters of illness in countries throughout the world, as would be typical for an infectious etiology.⁴⁻⁸ During a large outbreak in Japan, geographic wave-like spread of illness was clearly demonstrated, typical for an infection spread by the respiratory route.⁸ In concurrence to increase respiratory infections, KD has a higher incidence in winter-spring.⁹ The rarity of KD in adults suggests that virtually all adults experienced subclinical infection during childhood and subsequently developed a protective immune response. However, multiple studies over several decades have demonstrated that no known infectious agent can be implicated in KD etiology.¹⁰

There is a high prevalence of KD in Asian children, especially in Japan, Korea, China, and Taiwan, strongly supporting the hypothesis that genetic susceptibility determines host response to the KD pathogen(s) and therefore the prevalence of clinical illness. Recent data indicate that ~1 in 80 Japanese children and ~1 in 30 Taiwanese children develop KD during early childhood^{2,11}; these very high incidence rates strongly support the hypothesis that a very common (but presently unidentified) infectious agent results in KD and that Asian children are genetically predisposed. The fact that Asian children living a Western lifestyle in the U.S. have the same high incidence rates as those living in Asia supports a genetic predisposition rather than susceptibility based upon cultural practices or geographic location.

An environmental toxin as the cause of a generally non-recurring disease seems unlikely in the absence of its identification and purposeful removal from the environment. No environmental factors have been consistently associated with KD incidence.^{5,6,10,12} A recent study investigated association of KD with fine particulate air pollution and found that there was no clear association.¹³ Other recent studies have reported an apparent association between KD incidence and wind currents.^{14,15} One theory is that the wind might transmit a fungal toxin that could lead to KD.¹⁵ It appears that further clarification of the role of wind-borne transmission in KD etiology will be difficult until the etiologic agent(s) is identified.

A recent interesting study compared epidemiologic patterns of KD and other infectious diseases in children in Japan.¹⁶ The authors found that the mean patient age of KD and other viral infections, adjusted for the proportion of the population by age, was significantly negatively correlated with the total fertility rate; i.e. when the fertility rate was higher, the adjusted mean patient age was lower, implying that sibling-to-sibling transmission is likely an important factor in KD incidence. Moreover, these epidemiologic patterns were not consistent with transmission via a novel route such as a transcontinental wind. It was noted that there were significant fluctuations in the number of cases of the infectious diseases studied from year to year, with the exception of KD and exanthema subitum (due to human herpes virus 6 and 7, which are known to result in persistent infection). Substantial year-to-

year fluctuations would be predicted for infectious diseases with short incubation periods and no persistence of infection. A lack of substantial fluctuations in year-to-year incidence of an infectious disease occurs when the sum of the incubation period and infectious period of these diseases is high, as is observed with persistent infection.¹⁶ The authors concluded in this study that the epidemiology of KD points to an etiologic agent transmitted through close contact that remains asymptomatic in most hosts, with an estimated 1% of infections being symptomatic.¹⁶

Taken together, these epidemiologic findings best support the hypothesis that KD is caused by a common infectious agent that generally causes an asymptomatic infection, but leads to KD in children with underlying genetic predisposition.

Pathologic features

KD is a multi-systemic inflammatory illness, that particularly affects medium-sized muscular arteries and predominately the coronary arteries. KD arteriopathy is characterized by a three step vasculopathic processes: 1) acute necrotizing arteritis: a neutrophilic process which in the most severe cases results in necrosis of intima and media, leaving only a thin layer of adventitia to support the artery and leading to giant aneurysms, which can rarely rupture; 2) subacute/chronic arteritis: manifested by infiltration of lymphocytes, plasma cells, eosinophils, and macrophages; and, 3) luminal myofibroblastic proliferation: a process by which modified medial smooth muscle cells proliferate and can progressively obstruct the arterial lumen.¹⁷ All three processes can be observed in adjacent or non-adjacent segments of the same coronary artery, or can affect different coronary arteries.

A comprehensive study of the pathology of multiple organs and tissues in KD fatalities revealed inflammation in virtually all organ systems.¹⁸ This inflammation was non-purulent, and healed without apparent structural damage except in the arterial system. It was noted that inflammation subsided in most tissues by 6-8 weeks after the onset of illness, but persisted after the acute phase in various organs such as lung, spleen, salivary glands, and lymph nodes.¹⁸ This was compatible with the possibility of a persistent infectious agent. A high incidence of severe inflammatory lesions in the duct tissues (such as salivary gland duct, bile duct, pancreatic duct, prostatic duct and bronchus) led the authors to conclude that the illness preferentially affects the duct system and the vascular system.¹⁸ IgA plasma cells have been shown to be an important component of the vascular and the periductal inflammatory lesions.^{19,20}

These pathological findings, showing significant self-limited inflammatory infiltrates in many organs and tissues, are highly suggestive of a systemic infectious disease, such as a severe viral infection.^{21,22} The reason for persisting chronic arteritis in a subset of severely affected KD children¹⁷ is unclear, but could be due to a persisting infectious agent or to an epitope spreading effect, in which an initial immune response to an infectious agent transitions to target a self-antigen. It should be noted that despite some clinical similarities with KD, the pathologic features of the toxin- and superantigen-mediated illness *Staphylococcus aureus* toxic shock syndrome differ markedly from KD, and reveal hyaline

membranes in the alveoli, acute tubular necrosis of the kidney, and a lack of acute vasculitis.^{23,24}

Immunologic features

The initial neutrophilic predominance in peripheral blood and in KD arterial tissues is compatible with an innate immune response to an acute infection. T lymphocytic (primarily CD8 cell) and IgA plasma cell infiltrates can be identified in acutely inflamed KD coronary arteries, demonstrating robust acquired immune responses and suggesting that they are directed at an intracellular pathogen acquired at a mucosal site such as the respiratory tract.^{17,19,20,25} Although studies of selective expansion of V β 2 family T cell receptor expression in acute KD were reported,^{26,27} suggesting stimulation by a superantigen, this finding was not confirmed in other studies.^{28,29} B cell receptor sequencing of the IgA response in KD arteries revealed an oligoclonal or antigen-driven B cell response³⁰; sequencing of CD8+ T lymphocytes in peripheral blood of acute KD patients also revealed an oligoclonal CD8+ T cell response.³¹ These results strongly suggest an acquired immune response to specific antigens in KD children. Synthetic versions of KD oligoclonal antibodies detect antigen in medium-sized ciliated bronchial epithelial cells of KD patients but not infant controls, and also detect antigen in a subset of macrophages in inflamed KD tissues.³²⁻³⁴ The antigen detected by KD synthetic antibodies has not yet been specifically identified, likely because of the difficulty in obtaining the high-quality RNA and proteins from formalin-fixed, paraffin-embedded tissues needed for such identification. However, improved methods for detection of microbial nucleic acid and proteins from these tissues are emerging and should be useful in identifying specific KD antigen(s).^{35,36} Although acquired B cell responses are prominent in KD tissues, there is no evidence that immune complex deposition occurs or that autoantibodies play a role in disease pathogenesis.^{19,37,38} Rather, it appears most likely that the oligoclonal B cell and T cell responses are directed at the etiologic agent.

The robust acquired CD8+ T lymphocyte and IgA B lymphocyte immune responses that have been observed in acute KD tissues^{19,20,25,30,31,33,39} argue against the theory that KD is a primary disorder of innate immunity⁴⁰ and are highly suggestive of immune response to an infectious agent.

Ultrastructural features

Light and electron microscopy observations show that KD antigen detected by oligoclonal KD antibodies localizes to homogeneous intracytoplasmic inclusion bodies that appear to contain protein and RNA, most closely resembling inclusion bodies formed by viral protein and nucleic acid aggregates.^{34,41} Ultrastructural studies in KD tissues are limited by the fact that most tissue samples available for research studies are formalin-fixed and paraffin-embedded. However, in three KD lung samples that were formalin-fixed but not paraffin-embedded, ultrastructural morphology was partially preserved, and virus-like particles were observed in close proximity to the inclusion bodies.⁴²

Further investigation of the ultrastructure of the inclusion bodies will require collection of medium-sized ciliated bronchi from acute KD lungs from autopsy and fixation of the tissues in glutaraldehyde, which preserves ultrastructural morphology.⁴³

Transcriptional data

Upregulation of interferon-stimulated gene expression has been observed in acute KD lungs when compared with infant control lungs by real-time reverse transcriptase-PCR,⁴² strongly suggesting a cellular response to a viral infection. More notably, our recent high throughput RNA sequencing study of KD and control coronary arteries showed features of an antiviral immune response, such as activated cytotoxic T lymphocyte and type I interferon-induced gene upregulation in KD coronary arteries.³⁹ Significantly upregulated interferon-induced genes included IFI30, IFI44, IFI44L, IFIT2, MX1, MX2, OAS1, and OAS2, all of these are known to be induced by viral infection. In contrast, tumor necrosis family α genes were not differentially expressed in KD coronary arteries compared with childhood control coronary arteries.³⁹ Previous studies of the transcriptome of KD peripheral blood showed evidence of neutrophil activation, consistent with neutrophilic leukocytosis during the acute phase, but did not reveal an interferon signature, demonstrating the limitations of peripheral blood transcriptional profiling in delineating gene expression changes in diseased target tissues.^{44,45}

The identification of upregulated interferon-stimulated genes in both KD lung and coronary artery tissues provides additional support for the hypothesis of a viral etiology.

Could KD be caused by any infectious agent in genetically predisposed children?

As etiology of KD has not been elucidated despite various intensive efforts over decades, some investigators have proposed that there is no specific infectious cause of the disease. Instead, they postulate that children with a genetic predisposition can develop KD after experiencing any of a large number of different bacterial and/or viral infections.⁴⁶ By the very nature of this theory, it is difficult to disprove until a specific causative agent(s) is identified. However, the very distinctive clinical features of KD and the existence of epidemics and clusters of illness argue against this theory. Moreover, if KD is the result of infection with any infectious agent in a predisposed child, recurrences should be common with subsequent infectious triggers, which is not common in KD. The observation that a single synthetic KD monoclonal antibody, derived from IgA plasma cell B cell receptor sequences in KD arterial tissue, binds to ciliated bronchial epithelium in the majority of KD patients but not in infant controls argues for a specific etiologic agent and against the diverse etiologic agent hypothesis.³² Many childhood febrile illnesses with distinctive clinical features, such as polio, roseola, Fifth disease, and other infectious diseases such as acquired immunodeficiency syndrome, were thought to be due to multiple etiologic agents, but later found to be due to a single infectious agent.

Conclusion

The etiology of KD remains one of the major mysteries in the field of Pediatrics, and the lack of this knowledge has hampered improvements in diagnosis and management of this fascinating illness. Moreover, prevention will not be possible until the cause is identified. Researchers should continue to put in efforts in the direction of identification of etiology of KD, which will ultimately enable reductions in the morbidity and mortality from this important childhood illness.

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