Received: 18 October 2022 | Revised: 17 March 2023 | Accepted: 21 June 2023

DOI: 10.1111/1756-185X.14816

International Journal of Rheumatic Diseases WILEY

REVIEW

An update on understanding the pathophysiology in Kawasaki disease: Possible role of immune complexes in coronary artery lesion revisited

Saji Philip[1] | Ankur Jindal[2] | Raman Krishna Kumar[3]

[1]Tiruvalla Medical Mission Hospital, Tiruvalla, Kerala, India

[2]Department of Pediatric Clinical Immunology & Rheumatology, Post Graduate Institute of Medical Education, Chandigarh, Punjab, India

[3]Department of Pediatric Cardiology, Amrita Institute of Medical Sciences & Research Centre, Kochi, Kerala, India

Correspondence
Saji Philip, Division of Pediatric Cardiology, Tiruvalla Medical Mission Hospital, Pathanamthitta Dt., Tiruvalla, Kerala 689101, India; Aster Medicity Kochi, Kochi, Kerala, India.
Email: tfcsaji@yahoo.co.in; sajitfc@gmail.com

Abstract

Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown etiology affecting predominantly the coronary arteries. The role of circulating immune complexes (ICs) in the pathogenesis of KD has been studied using the sera of patients with KD. It has been proposed that ICs are triggered by single or multiple unknown causative agents as well as vasculitis. The outbreak of severe acute respiratory syndrome coronavirus 2 infections caused similar pathophysiology in producing vasculitis, and the RNA virus may have triggered signs and symptoms similar to KD. For clinicians and researchers alike, detecting the causative agents of KD remains a challenge. According to studies in animal models, type III hypersensitivity reactions caused by serum sickness are a prototype for IC vasculitis. The signs and symptoms of coronary artery dilation in swine are similar to those of KD. These models may be used to evaluate new pharmacological agents for KD. The pathogenesis of KD is complex and remains inadequately understood at present. However, circulating ICs may play a key role in the pathophysiology of KD and coronary artery vasculitis. Various therapeutic agents are being explored in the management of KD and these agents act at various stages of the production of pro-inflammatory cytokines and chemokines. In this review, we discuss recent developments in the pathogenesis of KD and provide insights into the innate immune response and mechanisms behind coronary artery damage in KD. We specifically explore the potential role of ICs in the pathogenesis of KD.

KEYWORDS
immune complex, immunopathogenesis, Kawasaki disease, vasculitis

1 | INTRODUCTION

In 1967, Dr. Tomisaku Kawasaki wrote a study titled "Mucocutaneous lymph node syndrome", which is today referred to as Kawasaki disease (KD).[1] KD is a childhood-onset, systemic, inflammatory illness that has a tendency to impact the coronary arteries. The cause of KD is still unknown. In high-income nations, KD is the most typical cause of acquired heart disease in young people.[1–3] KD-like sickness was described in patients who had coronavirus disease 2019 (COVID-19) during the most recent pandemic. The pandemic has shown that an infectious agent may be crucial in causing KD, primarily through the production of immunological complexes (ICs).[4] Despite the fact that the cause of KD is unknown, a double hit theory posits a viral trigger in a genetically predisposed individual.[5,6]

The clinical and epidemiological features of KD strongly suggest an infectious etiology, including the occurrence of epidemics, seasonal variation in incidence, and clustering of cases.[7] Unlike most infections, however, there are significant differences in racial predisposition that suggest a strong genetic influence. There is a possibility of triggering ICs by various infectious and non-infectious agents in the pathogenesis of KD. In the present review, we update on various studies that have shown the role of circulating ICs in the pathogenesis of KD.

2 | CIRCULATING IMMUNE COMPLEX

Antigen–antibody complexes are formed when antibodies are produced against a circulating or tissue antigen. The antigen may be exogenous from an infectious agent, toxin, or drug, or it may be endogenous, as occurs in autoimmune disorders. ICs are formed during many infectious and inflammatory diseases, and may play an important role in the immunopathogenesis of infectious and inflammatory processes. They are normally taken up by inflammatory cells through binding of the heavy chain constant region to immunoglobulin Fc Receptors (FcRs). Binding of immunoglobulin to some classes of FcRs (FcgRI, FcgRIIA, FcgRIIC, FcgRIIIA, FcgRIIIB) may lead to activation of inflammatory cells while binding to FcgRIIB results in suppression of inflammation. ICs may bind to FcRs and activate several inflammatory cells including monocytes, basophils, eosinophils, lymphocytes, and neutrophils.[8] Circulating ICs may have a definite role in understanding the immunopathogenic pathways that cause the symptoms and signs of vasculitis in KD.[9–14]

3 | PHYSIOLOGICAL AND PATHOLOGICAL ASPECTS OF CIRCULATING IMMUNE COMPLEXES

Immune complex production, in response to interaction of foreign substances with specific antibodies, constitutes an essential part of normal human immune defense mechanisms. This reaction is generally followed by one or more secondary reactions, all of which enable the body to neutralize and clear microorganisms and non-self-molecules (in the form of ICs after antibody binding) that have penetrated the various body barriers. Inactivation and elimination of these "invaders" prevents their deposition (localization) where they might multiply (in the case of microorganisms) or induce specific damage (toxins or enzymes).[14] IC formation followed by these secondary reactions (such as complement fixation) enhances macrophage system clearance mechanisms and prevents interaction with specific sites in the body that could be damaged by deposition. ICs do not normally accumulate in blood or organs, however, there are circumstances under which potentially pathogenic IC might form in the circulation and not be cleared properly. Factors that could influence this phenomenon and the manifestations of specific disease activity include the nature and quantity of the antigen and the antibody response, and the state of the systems involved in IC clearance.[14] There are a multitude of potential antigens (from whole organisms to small peptides), and the antibody response may vary with respect to class, subclass, affinity, etc. As a result, characteristics of ICs will be variable, and analysis of one IC system may not be applicable to other systems as well. For example, a patient with a monoclonal antibody against flavin became "yellow" because of the ubiquitous accumulation of flavin. Apparently, the antibody/flavin IC was cleared from the circulation at a much slower rate than flavin alone; the small IC (one antibody per IC) was too small to be cleared by the mononuclear phagocyte system, yet clearance of the flavin was apparently blocked by the antibody. The presence of autoantibodies to enzymes such as amylase, prostatic acid phosphatase, or creatine kinase can also block the clearance by a similar mechanism.[15]

At the opposite end of the spectrum are patients with mixed essential cryoglobulinemia. Large quantities of precipitating ICs (containing IgG and/or IgM, and specific antigens) are deposited at sites throughout the body, including the glomeruli.[16] These ICs can fix complement and cause local damage at their sites of deposition. The balance between rapid and safe clearance and tissue localization will then be influenced by factors that have been described in part in experimental studies but that have yet to be well defined in humans. These include the potential affinity of antibody or antigen for specific tissue (such as, DNA for glomerular basement membrane), and the hemodynamic and inflammatory status of the individual.[17] The specific immunochemical properties of the ICs, and in particular their potential to interact with FcRs and to fix complement, and react with complement receptors will fundamentally influence their ultimate fate and rate of clearance from the circulation.[13,18] IC formation and clearance cannot be a steady-state process; even during chronic serum sickness the concentrations of antigen, antibody, and IC formation may vary continuously.[13,16,17] Hence, ICs could form and deposit in a brief period of time. For example, patients with essential mixed cryoglobulinemia have sudden episodes of purpura over their legs and arms, and then their vasculitis subsides despite the presence of measurable ICs.[16]

4 | CIRCULATING IMMUNE COMPLEXES TRIGGERED BY INFECTIOUS AGENTS IN PATIENTS WITH KAWASAKI DISEASE

Circulating ICs, triggered by infectious agents, such as bacteria, viruses, or other unknown agents, have been detected in the early phase of patients with KD and, might be involved in the immunopathological mechanisms of development of vasculitis in these patients.[7,8] Although many pathogens have been implicated via superantigen toxins, such as staphylococcal and streptococcal toxic shock syndromes, other studies have failed to confirm these findings.[19,20] Several bacteria, including *Yersinia pseudotuberculosis*,[21] *Propionibacterium acnes*,[22] *Mycoplasma pneumoniae*,[23]

Chlamydia pneumoniae,[24] *Rickettsia* species,[25] and *Coxiella burnetii*,[26] and *Pseudomonas*;[27] viruses such as Epstein–Barr virus,[28] retroviruses,[29] adenovirus,[30] and measles virus;[31] and fungal agents such as *Candida* sp.[32] have been reported to be associated with KD. The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for COVID-19, is known to induce a systemic inflammatory response affecting multiple organs, with lungs being the most commonly and severely affected. Some of the extrapulmonary manifestations include involvement of the systemic vasculature, similar to KD. Several case reports have shown that SARS-COV-2 stimulates an immune reaction mimicking KD.[5] Singh et al. reported an association of KD with influenza.[33] Nakamura et al. reported that the pattern of KD was affected in 2009 after the epidemic of influenza A/H1N1 in Japan.[34] (The subtype H1N1 is distinguished by a mutation of hemagglutinin [H1] that affects the ability of the virus to infect cells, and a mutation of a neuraminidase [N1].) They observed a documented source of infection, both bacterial and viral, in one-third of patients with typical KD. Furthermore, Rowley et al. showed the presence of cytoplasmic inclusion bodies, which are compatible with viral protein aggregations and nucleic acid, in ciliated bronchial epithelium of patients with KD in the acute phase.[35] Considering the infectious cause for KD, a case–control study by Esper et al. suggested an association between human coronavirus—specifically New Haven (HCoV-NH)—infection and KD.[36] None of these reported viruses or bacteria have been convincingly replicated. The detection of circulating ICs in the sera of KD patients by different methods has been studied by various authors, and findings suggest definite triggering agents are behind the circulating ICs causing vasculitis.[37,38]

5 | HORSE-SERUM-INDUCED IMMUNE COMPLEX VASCULITIS IN SWINE

An attempt was made to produce IC vasculitis in swine, in the hope of producing an ideal experimental coronary artery disease animal model by administering a foreign protein, such as horse serum.[37,39] Philip et al. studied 21 pure-bred male piglets of 1.5, 2, and 3 months of age with normal saline and horse serum, and the results of clinical observations, hematoserology, echocardiography, and histopathology were very much similar to those in patients with KD. Two-dimensional echocardiogram of coronary arteries of piglets who received horse serum showed coronary intimal irregularities and aneurysmal dilatation (Figure 1A, B, D, E). Pericardial thickening as evidence of pericarditis was also observed (Figure 1C). A type III hypersensitive reaction was induced by antigen–antibody complexes that produced tissue damage through their capacity to activate a variety of serum mediators, principally the complement system. The localization of circulating IC in experimental serum sickness and the correlation of a possible IC mechanism in KD had already been studied by Knicker and Cochrane,[40] Fossard and Thompson,[41] and Cochrane.[42] Hence the clinical and histopathological findings of a systemic type III hypersensitivity reaction may mimic KD, and a possible similar mechanism may be involved in the pathogenesis of

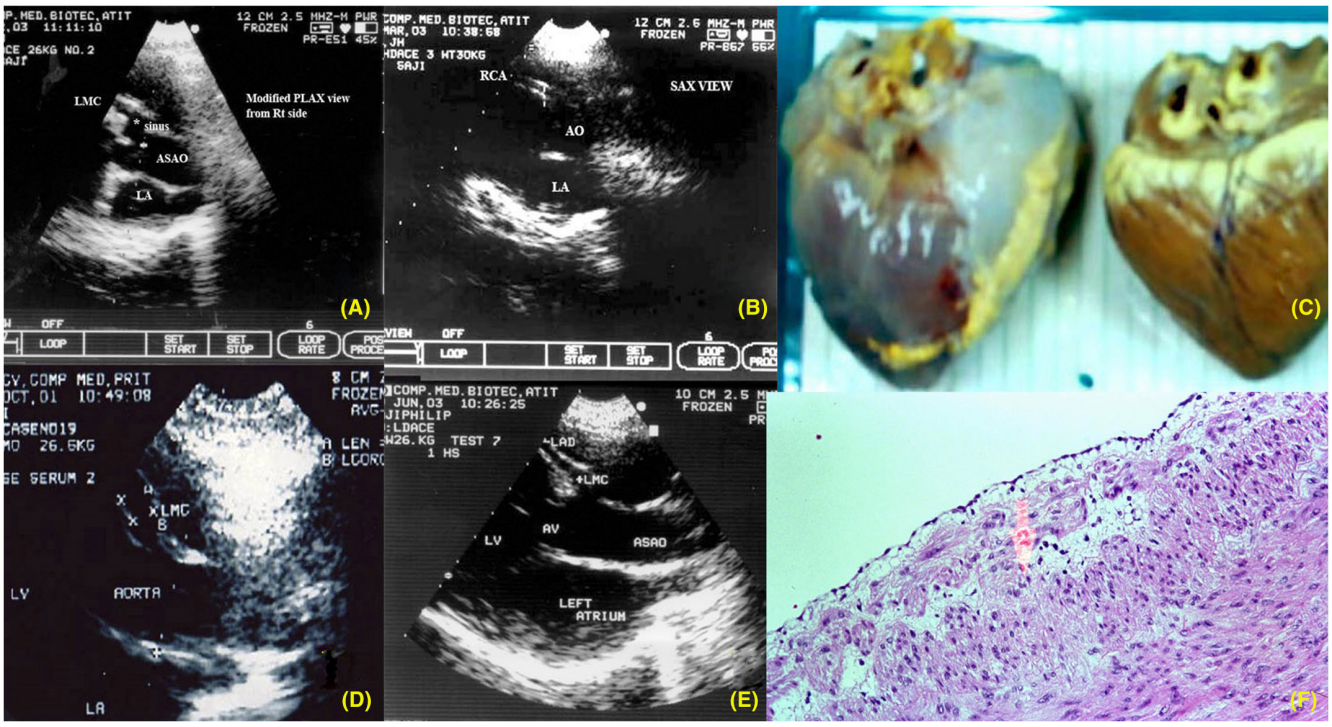

FIGURE 1 (A, B, D, E) Two-dimensional echocardiograms showing dilatation and intimal irregularities of proximal LAD in piglet that received HS on day 4. (C) Pericardial thickening and (F) hematoxylin & eosin staining of proximal LAD showing intimal and inner third of intima-medial proliferation with edematous changes at 14 days. Abbreviations: HS, horse serum; LAD, left anterior descending artery.

coronary arteritis in KD.[37,39] Possible mechanisms of ICs triggered by infectious and non-infectious agents damaging vascular endothelial cells are shown in Figure 2.

The pathology of KD has been studied in detail and ICs may play an important role in the pathogenesis of its vasculitis in swine.[37,38] Histopathology results after 14–60 days of horse serum infusion showed signs of subacute to chronic phases of arteritis, such as intimal proliferation, necrosis, vacuolization, and smooth muscle cell proliferation (Figures 1F and 3A–H).

Histopathology of specimens in the horse serum group revealed peri-arteritis, and pan-venulitis in the acute phase, including cellular infiltrations within myocardium (Figure 3D–F). Autopsy after 28 h showed more infiltrations than the 48-h specimen (Figure 3F). In contrast, the group given saline had normal coronary vessels (Figure 3A–C).

Albumin, which acted as an exogenous foreign protein antigen in the horse serum group, produces antigen–antibody complexes leading to a systemic hypersensitivity reaction. Onouchi et al. also reported that horse-serum-induced IC vasculitis in rabbit was very similar to the pathophysiology of coronary artery disease in KD.[43]

In all piglets, the changes were most significant in the tunica media, likewise the initial changes of the coronary arteries in KD, occurring in the tunica media at approximately 7–9 days after the onset of the disease, as reported by Naoe.[44] Vascular endothelial growth factor (VEGF) is one of the most important growth and survival factors for endothelium. It induces angiogenesis and endothelial cell proliferation and plays an important role in regulating vasculogenesis by increasing vascular permeability and vasodilation, partly through stimulation of nitric oxide synthase in endothelial cells.[45,46] VEGF can also stimulate cell migration and inhibit apoptosis. In humans, VEGF was significantly elevated during the acute phase of KD.[45] The presence of VEGF antigen that we observed in the tunica media and intimal regions of the coronary arteries in piglets is indirect evidence of vasculitis produced by horse serum infusion[39] (Figure 4). Immune complex vasculitis changes observed in the horse serum infusion study may serve as an ideal experimental animal model for coronary vasculitis mimicking KD, especially for testing the efficacy of pharmacological agents in the prevention of coronary artery aneurysms. ICs were also identified in the autopsy specimens of KD, suggesting that ICs might have played a role in producing the coronary artery changes in KD patients.[44,47] Inflammatory markers such as interleukin-6 (IL-6) and VEGFs are released by cells of the innate immune system such as monocytes, macrophages, and dendritic cells, leading to inflammation of vessels. It has been suggested that an autoantigen located in the walls of coronary arteries may serve as a target for these inflammatory cells and cytokines and lead to the development of coronary artery aneurysms in patients with KD.[47,48] However, this hypothesis is yet to be proven.

6 | INFECTIOUS TRIGGER IN THE PATHOGENESIS OF KAWASAKI DISEASE

Most cases of KD are self-limiting and have an uncomplicated course. Although the etiology of KD remains unknown, a double hit hypothesis involving an infectious trigger in a genetically predisposed individual is proposed.[8,40] Many viruses have been isolated from patients with KD, including adenovirus, Epstein–Barr virus, human immunodeficiency virus, and parvoviruses. Viruses are known to trigger a cascade of immune pathways in patients, such as activation of the cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) synthase (cGAS) pathway. cGAMP is one of the DNA sensors in the body that helps to identify foreign viral DNA material within cells. Once foreign DNA is detected, cGAS produces cGAMP that triggers the activation of stimulator of interferon genes (STING) within the endoplasmic reticulum, resulting in the release of cytokines and inflammatory molecules such as type 1 interferons (IFN) as part of the immune response towards the foreign infective agent. STING also acts on retinoic acid inducible gene-1 (RIG-1), an RNA sensor and mitochondrial antiviral signaling protein to detect viral RNA and trigger an immune response, indicating a role of the STING pathway in protecting against RNA viruses as well. The STING pathway has been found to be activated in KD and increased IFNs, neutrophils, and cytotoxic T cells have been reported in the histology of coronary artery tissue from patients with KD.

Apart from inducing inflammation, neutrophils, macrophages, and dendritic cells have also been found to invade the artery walls, causing damage because of their cytotoxic activity. There also appears to be an excessive activation of cytotoxic $CD8^+$ T cells, further supporting the possibility of an infectious agent as a trigger for the immune activation seen in KD.[5] Immune complexes have been reported in plasma and serum of patients with KD since 1977. They are seen within the first week of illness, gradually increase in number, and then wane after 3–4 weeks. This may suggest that ICs are formed in response to a foreign antigen to enhance the targeted action of other inflammatory cells and stimulate phagocytosis of the antigen to remove it from the circulation. Although this is an interesting finding, there has been no significant correlation between ICs and the severity of illness in KD patients, probably because of incomplete data collection and difficulties in identifying the phases of illness during which test samples were collected. More recent studies are needed to investigate the role of ICs in the pathogenesis of KD.[48] Excessive immune system activation may occur in KD, causing macrophage activation syndrome, a rare complication that can occur at any stage of KD and lead to increased cardiac complications and high mortality, highlighting the importance of timely diagnosis and management.[49]

Studies have shown that this immune response is strongest during the first few weeks of infection with many inflammatory molecules such as cytokines and C-reactive protein being released into the bloodstream. This could be related to the increased expression of cytokines such as IL-1, IL-6, and IL-8.[48] Tumor necrosis factor-α (TNF-α) levels are raised more significantly in patients with KD who develop coronary artery aneurysms compared with those without. This could be related to TNF-α triggering the release of chemokines by endothelial cells, increasing the

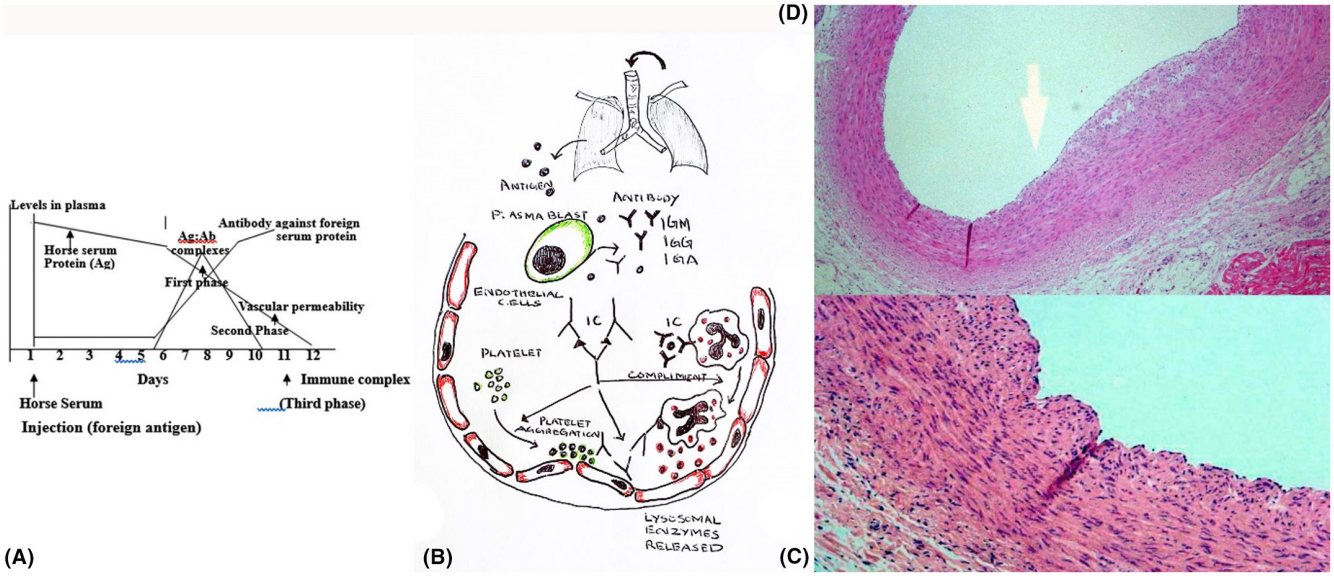

FIGURE 2 (A–D) Induction of IC vessel wall injury. (A) Three sequential phases in induction of systemic type III sensitive reaction by horse serum. (B) Composite of drawing depicts mechanism of IC vessel wall injury. Antigen possibly enters through the respiratory tract as an unknown infectious or non-infectious agent producing specific antibodies from plasmablast. Further formation of IC leads to a cascade of platelet aggregation, release of lysosomal enzymes from the neutrophils, complement fixation, and damage to the endothelium. (C, D) Histopathological changes occurring in proximal left anterior descending artery show (hematoxylin & eosin stain) intimal proliferation (C) and intimal and inner third medial proliferation induced by horse serum-mediated IC coronary changes. Abbreviations: Ag:Ab, antigen to antibody; IC, immune complex.

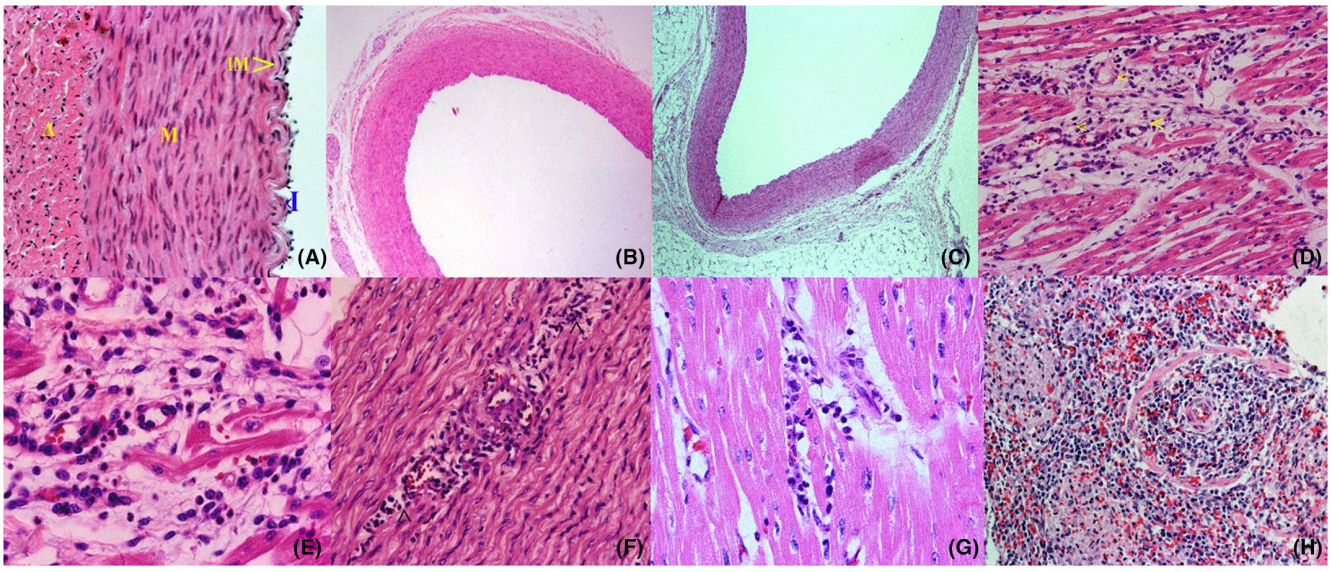

FIGURE 3 (A–H) Histopathology of coronary arteries (H&E staining) of HS-induced coronary vasculitis in the saline and HS groups of swine. (A–C) Normal coronary arterial walls after three doses of normal saline infusions in the saline group. (A) Left coronary artery (400×) at day 41 showing normal intima (I), internal elastic membrane (IM), tunica media (M), and adventitia (A); (B) left coronary artery (40×) at 40 days; (C) left anterior descending artery (40×) at day 24 appeared normal. (D–H) H&E staining of coronary arterial walls of piglets in the HS group. (D, E; 2–4 days) Perivenular cellular infiltrates of the coronary vein and vasa vasorum (<) (200×) and diffuse cellular infiltrates in the tunica media (400×) at day 3. (F) Cellular infiltrates in the tunica media (200×) of the ascending aorta at day 2. (G) Diffuse cellular infiltrates in the myocardium (400×) and (H) in the distal tubular areas of the right kidney (200×) at day 2. Abbreviations: H&E, hematoxylin & eosin; HS, horse serum.

permeability of the endothelial lining to other inflammatory cells such as neutrophils and causing more severe damage to the affected arteries. Superantigen binds to T-cell receptor, inducing the release of immune mediators IL-6, TNF-α, and transforming growth factor-β. Identification of $CD8^+$ T lymphocyte, IgA plasma cells, and macrophages in the coronary arteries suggest a viral

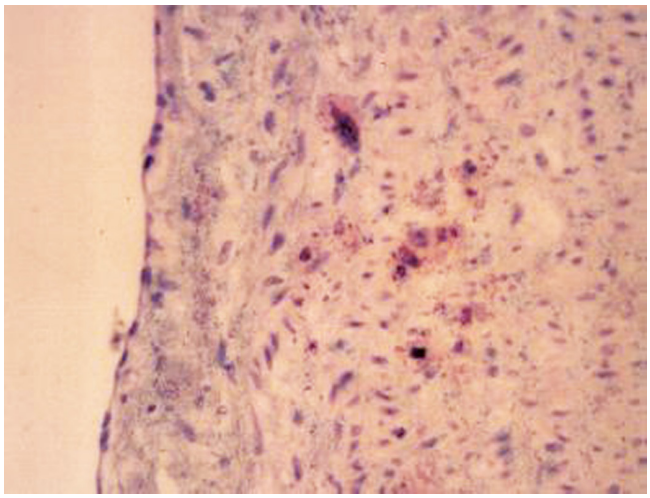

FIGURE 4 Avidin–biotin peroxidase staining for VEGF. Left main coronary artery at day 24 after three HS infusions in piglet showing positive immunoreactivity for VEGF (brownish aggregates and spots) diffusely in intimal regions and tunica media. Magnification: ×200. Abbreviations: HS, horse serum; VEGF, vascular endothelial growth factor.

etiology.[47,48] Hence both infections and immune component actively take part in the pathogenesis of KD.

7 | KAWASAKI DISEASE-LIKE ILLNESS IN SARS-CoV-2 INFECTIONS

A small proportion of children exposed to SARS-CoV-2 develop principal KD symptoms that fulfil the diagnostic criteria for KD in Europe and the USA.[50–52] This is the first virus to be consistently and reproducibly associated with the development of principal KD symptoms in multiple areas even with low rates. Systemic inflammation is the most striking finding in some patients SARS-CoV-2 infection, which causes a viral disease with inflammation and infection of endothelial cells.

There are several hypotheses on how the virus might induce inflammation. Pyroptosis, related to viral infection and replication in airway epithelial cells, leads to cytokine release and consequent vascular leakage. As expected, IL-1β, released during pyroptosis, results in elevated cytokine during SARS-CoV-2 infection. Viral infection of monocytes and macrophages can also result in aberrant cytokine production. These pro-inflammatory cytokines and chemokines, including IL-6 and IFN-γ, play an important role in inducing and modulating an array of immune responses; monocyte chemoattractant protein-1 and IFN-γ-induced protein 10 kDa attract immune cells, notably monocytes and T lymphocytes, but not neutrophils. SARS-CoV-2-infected patients also exhibit high levels of IFN-γ and IL-18, which are key players in the cytokine storm syndrome. It has been suggested that the induction of apoptosis and pyroptosis (representing a form of cell death that is triggered by pro-inflammatory signals and associated with inflammation) might have an important role in endothelial cell damage in patients with SARS-CoV-2.[53–55] Massive production of damage-associated molecular patterns from cell death and oxidative stress in the circulating blood exert pleiotropic effects on platelets, monocytes, neutrophils, endothelial cells, and vascular smooth muscle cells through receptor-mediated (e.g. the lectin-like oxidized low-density lipoprotein [LDL] receptor-1) and receptor-independent mechanisms. Inflammation and oxidative stress mutually amplify each other, possibly leading to the induction of KD. Both KD and a subset of multisystem inflammatory syndrome in children (MIS-C) fulfilling the diagnostic criteria for KD show some common but distinct pathophysiological features. Further study will be necessary to find out whether the strategy for the diagnosis and treatment of KD may be useful in the management of a subset of MIS-C fulfilling the diagnostic criteria for KD.[56] SARS-CoV-2 can be a trigger for IC mechanism initiation and produces KD-like illness.

8 | CIRCULATING PLATELET–NEUTROPHIL AGGREGATES PLAY A SIGNIFICANT ROLE IN KD

Platelet activation at the site of inflamed endothelium contributes to vascular inflammation and vascular wall remodeling. Released chemokines from activated platelets, such as platelet factor 4, CXCL7, and β-thromboglobulin, have important effects on vascular inflammation. Vascular injury may lead to increased platelet activation with neutrophil and monocyte infiltration, as well as increased platelet adhesion and aggregation through the release of inflammatory cytokines. Circulating platelet–neutrophil aggregates amplify acute inflammation and exhibit a hyper-reactive response that could promote the development of thrombotic and inflammatory disease, obstruct the flow of coronary micro-vessels, and contribute to vascular inflammation and tissue injury. Likewise, activated platelets and neutrophils have been demonstrated during the acute phase of KD-associated inflammation and may contribute to the occurrence of coronary artery aneurysm.[57,58] Therapeutic inhibition of platelet–neutrophil aggregates reduces neutrophil recruitment and permeability and may help to attenuate organ damage and mitigate the inflammatory process. Corticosteroids may cause inhibition of platelet adhesion, spreading, aggregation, thrombus formation, and the interaction of platelets with monocytes through regulation of P2Y12 receptor signaling, which is the main platelet receptor responsible for ADP-induced platelet activation. Hence, prednisolone has a role in helping to control vascular and thrombotic diseases.

The use of corticosteroids as part of a combination treatment may have a beneficial effect on terminating the inflammatory process through its anti-inflammatory properties, which suppress immune cell activation, proliferation, and cytokine production, as well as through its ability to decrease endothelial expression of cellular adhesion molecules in the acute phase of KD. However, previous

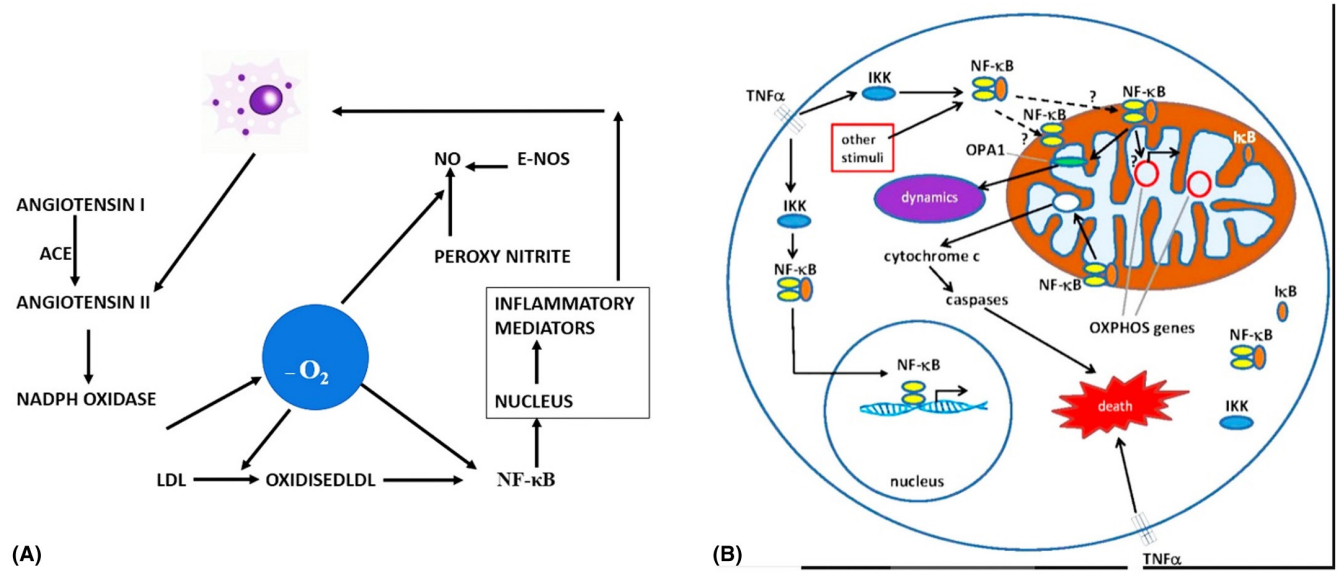

FIGURE 5 (A) Role of macrophages and various processes in release of singlet oxygen leading to inflammatory mediators through NF-κB. (B) Role of TNF-α in the production of NF-κB at the mitochondrial level leading to inflammatory cascade with cellular death. Abbreviations: ACE, angiotensin-converting enzyme; AT II, angiotensin II; e-Nos, endothelial nitric oxide; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, transcription factor nuclear factor-κB; NO, nitric oxide.

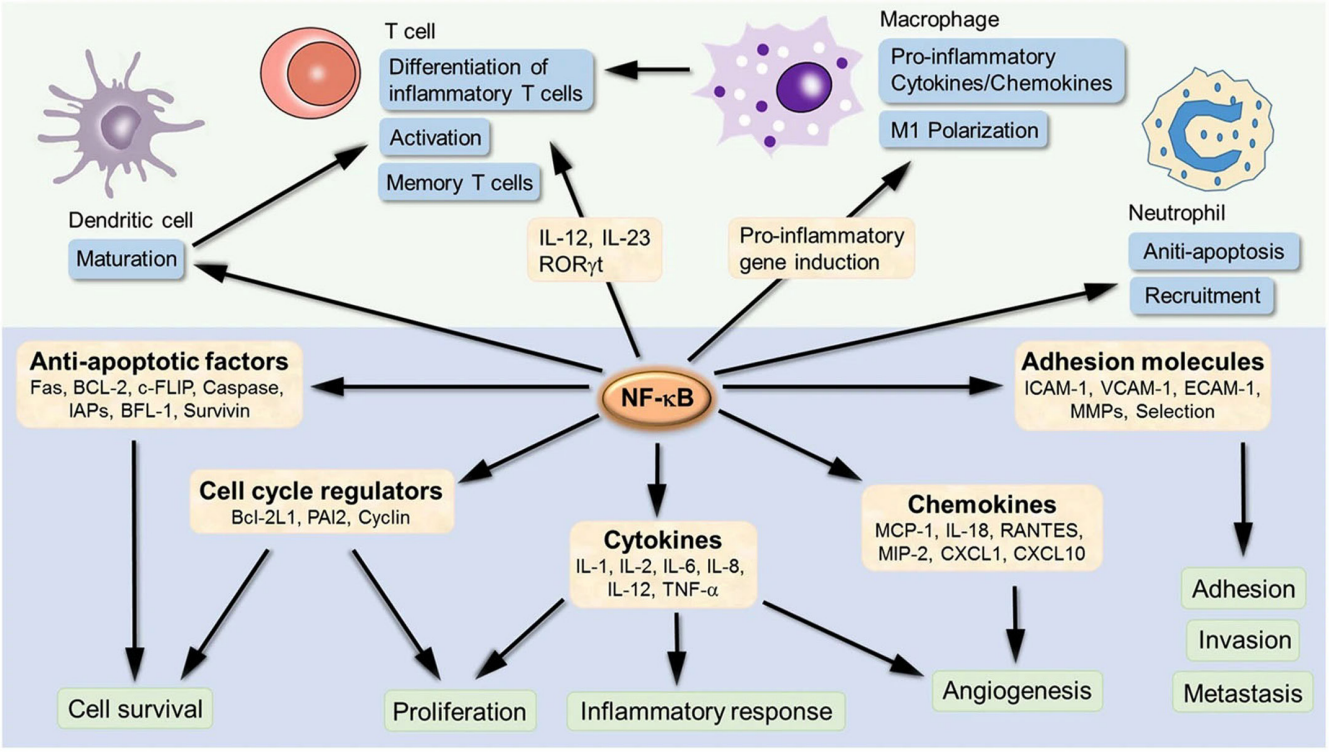

FIGURE 6 NF-κB target genes involved in inflammation development and progression. NF-κB is an inducible transcription factor. After its activation, it can activate transcription of various genes and thereby regulate inflammation. NF-κB targets inflammation not only directly by increasing the production of inflammatory cytokines, chemokines, and adhesion molecules, but also by regulating the cell proliferation, apoptosis, morphogenesis, and differentiation. Abbreviation: NF-κB, transcription factor nuclear factor-κB.

studies have suggested that the use of corticosteroids for patients with KD should be limited because such treatment may be linked to a higher incidence of coronary artery abnormalities and impaired vascular remodeling. The main benefit of corticosteroid combination treatment is considered to be early suppression of the vasculitis that precedes vascular remodeling.[57]

9 | PATHWAYS FOR NUCLEAR FACTOR-κB SIGNALING IN THE CYTOPLASM AND THE MITOCHONDRION

Macrophages play a key role in the inflammatory process. Angiotensin II in turn releases nicotinamide adenine dinucleotide phosphate (NADPH), a required cofactor for CYP-mediated biotransformation, and oxygen serves as a substrate. Singlet oxygen releases from the NADPH oxidase and singlet oxygen converts LDL to oxidized LDL, which in turn releases the transcription factor nuclear factor-κB (NF-κB), regulates multiple aspects of innate and adaptive immune functions, and serves as a pivotal mediator of inflammatory responses (Figures 5 and 6).

The NF-κB tri-subunit complex exists in an inactive state in the cytoplasm. NF-κB activation is initiated by TNF-α binding to TNF receptors. Intrinsic apoptotic pathway stimulation by NF-κB activation in mitochondria leads to cytochrome c release, thus triggering caspase cascades and programmed cell death. NF-κB induces the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines, and also participates in inflammasome regulation.[59] In addition, NF-κB plays a critical role in regulating the survival, activation, and differentiation of innate immune cells and inflammatory T cells. Consequently, deregulated NF-κB activation contributes to the pathogenic processes of various inflammatory diseases (Figure 6).[60]

10 | ROLE OF ANTIOXIDANTS IN MITIGATION OF VASCULITIS

The goal of initial management in KD is to reduce inflammation; intravenous γ-globulin and aspirin form the standard regimen, and a multicenter randomized controlled trial in the USA demonstrated the effectiveness of this combination in lowering coronary artery lesions in KD. Antioxidants can reverse endothelial dysfunction induced by methionine and restore the endothelial function in hyperlipidaemia, and they can also slow down the thickening of arteries. A trial of antioxidants in the prevention of coronary artery disease in horse serum-mediated vasculitis in a swine model showed the potential relevance of early treatment in mitigation of coronary arteritis in KD.[61] The role of antioxidants in protection against cardiovascular disease prevents endothelial dysfunction in humans by regulating endothelial nitric oxide (NO) levels as well as by inhibiting cardiovascular inflammation, lipid peroxidation, platelet aggregation, and LDL oxidation.[62] Unpublished data of

TABLE 1 Intervention in coronary artery disease by various therapeutic agents and its possible mechanisms, acting at different stages in the production of pro inflammatory cytokines and chemokines.

Intravenous immunoglobulin	Neutralization of bacterial super-antigens and other infectious agents, and pathogenic autoantibodies. Inhibition of production of TNF-α. Suppression of production of pro-inflammatory cytokines. Modulation of cytokine production. Neutralization of toxins. Enhancement of regulatory T cells. Inhibition of differentiation of Th17 cells Antioxidative effects (reduction of NO production by neutrophils)
Infliximab	TNF-α receptor antagonists. Infliximab is a chimeric monoclonal IgG antibody that targets transmembrane TNF-α. Inhibition of TNF-α in turn prevents NF-κB, so that various mechanisms at molecular level such as proliferation, inflammatory responses, angiogenesis, pro-inflammatory cytokines/chemokines, and apoptosis can be prevented
Etanercept	Etanercept is a soluble fusion protein receptor that works more broadly on TNF (both TNF-α and lymphotoxin), and binds to only circulating TNF-α, not at the transmembrane TNF-α, thereby avoiding the adverse effects seen in infliximab
Antioxidants	Vitamins A, C, and E can scavenge singlet oxygen, inhibition of LDL to oxidized LDL and in turn to NF-κB can be prevented. Vitamin C can prevent eNOS to peroxynitrate with the help of $O2^{-}$
Statins	Prevention of LDL to oxidized LDL, and angiotensin II to NADPH oxidase
Aspirin	Important anti-inflammatory activity (at high doses) and antiplatelet activity (at low doses)
Ulinastatin	Urinary trypsin inhibitor and has a property to inhibit neutrophil elastase
Methotrexate	A folic acid antagonist suppresses lymphocyte proliferation and has a role in modulating cytokines, especially IL-6, highly expressed in KD. Inositol triphosphate 3-kinase C acts as a negative regulator of T-cell activation and activated T cells may play a pivotal role in pathogenesis of KD
Cyclosporin	Suppresses the activity of T cells
Doxycycline	Inhibits T-cell activation and TNF-α production in peripheral immune cells and also inhibits directly MMP-9 enzymatic activity derived from TNF-α-stimulated vascular smooth muscle cells. Hence, doxycycline can mitigate TNF-α-induced MMP-9-mediated coronary elastin breakdown and improve coronary outcome
Methyl prednisolone	Acts in various ways to decrease the inflammatory cycle including: dampening the inflammatory cytokine cascade, inhibiting the activation of T cells, decreasing the extravasation of immune cells into the central nervous system, facilitating the apoptosis of activated immune cells, and indirectly decreasing the cytotoxic effects of nitric oxide and TNF-α
Anakinra	It acts by blocking both IL-1α and IL-1β. It is an IL-1 receptor antagonist that blocks the biological activity of natural IL-1 by competitively inhibiting the binding of IL-1 to IL-1 type receptor

Abbreviations: eNOS, endothelial nitric oxide synthase; IL, interleukin; KD, Kawasaki disease; LDL, low-density lipoprotein; MMP-9, matrix metalloproteinase-9; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-κB; NO, nitric oxide; Th17; T helper type 17; TNF-α, tumor necrosis factor-α.

antioxidant trials include the vitamin E, A, and C trial in patients with KD, which was found to be quite successful in mitigating vasculitis in both signs and symptoms.

Reactive oxygen species generated by activated polymorphoneutrophils are directly toxic to endothelial cells and are a potent cause of endothelial cell damage. The role of antioxidants in protection against cardiovascular disease prevents endothelial dysfunction in humans by regulating endothelial NO levels as well as by inhibiting cardiovascular inflammation, lipid peroxidation, platelet aggregation, and LDL oxidation.[63] Chain-breaking antioxidants such as vitamins C and E are powerful reductants that scavenge free radical species to prevent further oxidation. Phagocytic cells, including neutrophils and macrophages, generate NO via NO synthase, which is inducible by immunological stimuli such as endotoxin (lipopolysaccharides) and various cytokines.[63,64] The broader role of NO in the inflammatory response is not well established, although the reactivity of NO or its potential conversion product, peroxynitrite anion, with sulfhydryl groups indicates the possibility of cellular biochemical targets, the alteration of which would put tissue at risk. The protective effects of NO synthase in IC-induced vasculitis were also studied by Mulligan et al.[64] There is increasing evidence that lipoprotein oxidation plays an important role in vascular endothelial damage and atherosclerosis.[64] LDL to oxidized LDL can be reduced by administration of vitamin C, E, statin, and peroxisome proliferator-activated receptor (PPAR) agonists. They are used for the treatment of symptoms of the metabolic syndrome, mainly for lowering triglycerides and blood sugar). In the same way, NF-κB and NADPH oxidase can be reduced by giving statin and PPAR agonist. Vitamin C and statin have a role in reducing the release of singlet oxygen from endothelial NO (Figure 5). TNF-α and NF-κB inhibitors can stop apoptosis or cellular damage in the coronary endothelium (Figure 6). Inflammation and oxidative stress mutually amplify each other, and possibly lead to the induction of KD. In order to suppress procytokines, and stop further inflammation at different points along the pathways of KD coronary artery disease, new therapeutic medicines must be developed. As shown in Table 1, various treatment drugs and their potential mechanisms act at various points along the pathways that lead to the generation of pro-inflammatory cytokines and chemokines.

11 | CONCLUSIONS

The specific etiology remains inadequately understood in KD. However, circulating ICs triggered by various etiological agents play a key role in the pathogenesis of coronary vasculitis in KD. Horse-serum-induced type III hypersensitivity reaction in swine indicates that serum sickness is a prototype of IC vasculitis, and the signs and symptoms of coronary artery dilation in swine resemble those of KD. Therefore, interrupting IC formation through treatment trials either in isolation or in combination, targeting various steps in the pathogenesis of coronary artery lesions, such as the production of inflammatory cytokines, chemokines, TNF-α, NO, bacterial superantigens, and specific pathogenic autoantibodies, will give hope for mitigating coronary artery lesions in KD.

AUTHOR CONTRIBUTIONS

Dr. Ankur Jindal; active discussions on SARS coV2 and KD like illness and possible etiology. Also Flow chart discussion with role of Immune complexes and editing. Dr. Raman Krishna Kumar; active discussions on role of immune complexes, various stages of proinflammatory cytokines, and therapeutic challenges and reediting discussions. All authors have reviewed this paper and its content.

ACKNOWLEDGEMENTS

We are grateful to Prof. Ming-Tai, Department of Pediatrics, Division of Pediatric Cardiology, National Taiwan University Hospital, Taipei, Taiwan for active discussions on the role of immune complexes in KD.

CONFLICT OF INTEREST STATEMENT

No personal conflicts of interest of any of the authors including copy right trasfer. Also no funding or grant or industrial support or from any other sources for the prepration of this paper.

DATA AVAILABILITY STATEMENT

All authors have reviewed this paper and its content. No personal conflicts of interest of any of the authors including copy right transfer. Also no funding or grant or industrial support or from any other sources for the preparation of this paper.

ORCID

Saji Philip https://orcid.org/0000-0003-2674-7738
Ankur Jindal https://orcid.org/0000-0002-7954-0661
Raman Krishna Kumar https://orcid.org/0000-0003-4343-0951

REFERENCES

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children: clinical observations of 50 cases. *Arerugi*. 1967;16:178-222.
2. Burns JC, Glodé MP. Kawasaki syndrome. *Lancet*. 2004;364:533-544. doi:10.1016/S0140-6736(04)16814-1
3. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. *J Am Coll Cardiol*. 2016;67:1738-1749.
4. Menikou S, Langford PR, Levin M. Kawasaki disease: role of immune complexes revisted. *Front Immunol*. 2019;10:1156-1166.
5. Fang Y, Aravamudan VM, Sridharan GK, Mehta KK, Sekhar R, Senguttuvan NB. Kawasaki like illness due to COVID-19: a review of the literature. *J Infect Dev Ctries*. 2021;15(5):630-638. doi:10.3855/jidc.14185
6. Fossard C, Thompson RA. Mucocutaneous lymph-node syndrome (Kawasaki disease): probable soluble complex disorder. *BMJ*. 1977;1:883-884.
7. Makino N, Nakamura Y, Yashiro M, et al. Epidemiological observations of Kawasaki disease in Japan, 2013-2014. *Pediatr Int*. 2018;60:581-587.
8. Pachman LM, Herold BC, Davis AT, et al. Immune complexes in Kawasaki syndrome: a review. *Prog Clin Biol Res*. 1987;250:193-207.

9. Weindling AM, Levinsky RJ, Marshall WC, Hood J. Circulating immune complexes in mucocutaneous lymph-node syndrome (Kawasaki disease). *Arch Dis Child*. 1979;54:241-242.
10. Furuse A, Matsuda I. Circulating immune complex in the mucocutaneous lymph node syndrome. *Eur J Pediatr*. 1983;141:50-51.
11. Mason WH, Jordan SC, Sakai R, Takahashi M, Bernstein B. Circulating immune complexes in Kawasaki syndrome. *Pediatr Infect D*. 1985;4:48-51.
12. Li CR, Yang XQ, Shen J, Li YB, Jiang LP. Immunoglobulin G subclasses in serum and circulating immune complexes in patients with Kawasaki syndrome. *Pediatr Infect Dis*. 1990;9:544-547.
13. Shirai N, Yabana T, Ueda M. Pathology of Kawasaki disease. *Nippon Rinsho*. 2008;66:251-257.
14. Schifferli JA, Taylor RP. Physiological and pathological aspects of circulating immune complexes. *Kidney Int*. 1989;35:993-1003.
15. Fari-Iangi M, Osserman EF. Myeloma with xanthoderma due to an IgG lambda monoclonal anti-flavin antibody. *N Engl J Med*. 1976;294:177-183.
16. Ponticelli C, D'amico G. Essential mixed cryoglobulinemia. In: Schrier RW, Gottschalk CW, eds. *Diseases of the Kidney*. 4th ed. Little Brown & Co; 1988:2377-2392.
17. Couser WG. Mechanisms of glomerular injury in immune-complex disease. *Kidney Int*. 1985;28:569-583.
18. Couser WG, Baker PJ. Adler: complement and the direct mediation of immune glomerular injury: a new perspective. *Kidney Int*. 1985;28:879-890.
19. Xu SX, McCormick JK. Staphylococcal superantigens in colonization and disease. *Front Cell Infect Microbiol*. 2012;2:52.
20. Gupta-Malhotra M, Viteri-Jackson A, Thomas W, Zabriskie JB. Antibodies to highly conserved peptide sequence of staphylococcal and streptococcal superantigens in Kawasaki disease. *Exp Mol Pathol*. 2004;76:117-121. doi:10.1016/j.yexmp.2003.12.003
21. TaharaM BK, Waki K, Arakaki Y. Analysis of Kawasaki disease showing elevated antibody titres of Yersinia pseudotuberculosis. *Acta Paediatr*. 2006;95:1661-1664. doi:10.1080/08035250600750080
22. TomitaS,KatoH,FujimotoT,InoueO,KogaY,KuriyaN.Cytopathogenic protein in filtrates from cultures of Propionibacterium acnes isolated from patients with Kawasaki disease. *Br Med J*. 1987;295:1229-1232. doi:10.1136/bmj.295.6608.1229
23. Ebrahim M, Gabay M, Rivas-Chacon RF. Evidence of acute mycoplasma infection in a patient with incomplete and atypical Kawasaki disease: a case report. *Case Rep Med*. 2011;2011:606920. doi:10.1155/2011/606920
24. Normann E, Naas J, Gnarpe J, Backman H, Gnarpe H. Demonstration of chlamydia pneumoniae in cardiovascular tissues from children with Kawasaki disease. *Pediatr Infect Dis J*. 1999;18:72-73. doi:10.1097/00006454-199901000-00020
25. Carter RF, Haynes ME, Morton J. Rickettsia-like bodies and splenitis in Kawasaki disease. *Lancet*. 1976;2:1254-1255. doi:10.1016/S0140-6736(76)91192-2
26. Weir WR, Bouchet VA, Mitford E, Taylor RF, Smith H. Kawasaki disease in European adult associated with serological response to Coxiella burnetii. *Lancet*. 1985;2:504. doi:10.1016/S0140-6736(85)90440-4
27. Keren G. Wolman M can pseudomonas infection in experimental animals mimic Kawasaki disease. *J Infect Dis*. 1984;9:22-29.
28. Muso E, Fujiwara H, Yoshida H, et al. Epstein-Barr virus genome-positive tubulointerstitial nephritis associated with Kawasaki disease-like coronary aneurysms. *Clin Nephrol*. 1993;40:7-15.
29. Burns JC, Geha RS, Schneeberger EE, et al. Polymerase activity in lymphocyte culture supernatants from patients with Kawasaki disease. *Nature*. 1986;323:814-816. doi:10.1038/323814a0
30. Okano M, Thiele GM, Sakiyama Y, Matsumoto S, Purtilo DT. Adenovirus infection in patients with Kawasaki disease. *J Med Virol*. 1990;32:53-57. doi:10.1002/jmv.1890320109
31. Schulz TF, Hoad JG, Whitby D, Tizard EJ, Dillon MJ, Weiss RA. A measles virus isolate from a child with Kawasaki disease: sequence comparison with contemporaneous isolates from 'classical' cases. *J Gen Virol*. 1992;73:1581-1586. doi:10.1099/0022-1317-73-6-1581
32. Murata H. Experimental Candida- induced arteritis in mice: relation to arteritis in the mucocutaneous lymph node syndrome. *Microbiol Immunol*. 1970;23:825-831.
33. Banday AZ, Arul A, Vignesh P, Singh MP, Goyal K, Singh S. Kawasaki disease and influenza-new lessons from old associations. *Clin Rheumatol*. 2021;40:2991-2999. doi:10.1007/s10067-020-05534-1
34. Nakamura Y, Yashiro M, Uehara R, et al. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2007–2008. *J Epidemiol*. 2010;20:302-307. doi:10.2188/jea.je20090180
35. Rowley AH, Baker SC, Shulman ST, et al. Cytoplasmic inclusion bodies are detected by synthetic antibody in ciliated bronchial epithelium during acute Kawasaki disease. *J Infect Dis*. 2005;192:1757-1766. doi:10.1086/497171
36. Esper F, Shapiro ED, Weibel C, et al. Association between a novel human coronavirus and Kawasaki disease. *J Infect Dis*. 2005;191:499-502. doi:10.1086/428291
37. Philip S, Lee WC, Wu MH, Mammen CK, Lue HC. Histopathological evaluation of horse serum-induced immune complex vasculitis in swine: implication to coronary artery lesions in Kawasaki disease. *Pediatr Neonatol*. 2014;55:297-305.
38. Sawa F. Circulating immune complexes in MCLS. *Acta Paed Jap*. 1979;83:493-498.
39. Philip S, Lee WC, Liu SK, Wu MH, Lue HC. A swine model of horse serum-induced coronary vasculitis: an implication for Kawasaki disease. *Pediatr Res*. 2004;55:211-219.
40. Knicker WT, Cochrane CG. The localization of circulating immune complex in experimental serum sickness. *J Exp Med*. 1968;127:119-135.
41. Fossard C, Thompson RA. Mucocutaneous lymph-node syndrome (Kawasaki disease): probable soluble complex disorder. *Br Med J*. 1977;1(6065):883. doi:10.1136/bmj.1.6065.883
42. Cochrane CG. Mechanisms involved in the deposition of immune complex in tissues. *J Exp Med*. 1971;134:755-758.
43. Onouchi Z, Ikuta K, Nagamatsu K, Tamiya H, Sakakibara Y, Ando M. Coronary artery aneurysms develop in weanling rabbits with serum sickness but not in mature rabbits: an experimental model for Kawasaki disease in humans. *J Vasc Dis*. 1995;46:679-686.
44. Naoe S. Pathology of coronary aneurysms in the young. Abstract (CS12) Presented at the 10th Asian Congress of Pediatrics, Taipei, Taiwan 2000.
45. Hausner EA, Orsini JA, Foster LL. Vascular endothelial growth factor in porcine coronary arteries following balloon angioplasty. *J Invest Surg*. 1999;12:15-23.
46. Terai M, Yasukawa K, Narumoto S, Taeno S, Oana S, Kohno Y. Vascular endothelial growth factor in acute Kawasaki disease. *Am J Cardiol*. 1999;83:337-339.
47. Yeung RS. Pathogenesis and treatment of Kawasaki's disease. *Curr Opin Rheumatol*. 2005;17:617-623. doi:10.1097/01.bor.0000174184.15901
48. Menikou S, Langford PR, Levin M. Kawasaki disease: the role of immune complexes revisited. *Front Immunol*. 2019;10:1156.
49. García-Pavón S, Yamazaki-Nakashimada MA, Báez M, Borjas-Aguilar KL, Murata C. Kawasaki disease complicated with macrophage activation syndrome: a systematic review. *J Pediatr Hematol Oncol*. 2017;39:445-451.
50. Toubiana J, Poirault C, Corsia A, et al. Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. *BMJ*. 2020;369:m2094.
51. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the

SARS-CoV-2 epidemic: an observational cohort study. *Lancet*. 2020;395:1771-1778.
52. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA*. 2020;324:259-269.
53. Suowen X, Chen M, Weng J. Letter to editor. COVID-19 and Kawasaki disease in children. *Pharamacol Res*. 2020;159:104951. doi:10.1016/j.phrs.2020.104951
54. La Torre F, Leonardi L, Giardino G, et al. Immunological basis of virus-host interaction in COVID-19. Immunology Commission of the Italian Society of pediatric allergy, immunology (SIAIP). *Pediatr Allergy Immunol*. 2020;31:75-78. doi:10.1111/pai.13363
55. Mehta P, Mcauley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033-1034.
56. Amirfakhryan H. Kawasaki-like disease in children with COVID-19: A hypothesis. *Med Hypotheses*. 2020;143:110117. doi:10.1016/j.mehy.2020.110117
57. Hara T, Yamamura K, Sakai Y. The up-to-date pathophysiology of Kawasaki disease. *Clin Transl Immunol*. 2021;10(5):e1284. doi:10.1002/cti2.1284
58. Ueno K, Nomura Y, Morita Y, Eguchi T, Masuda E, Kawano Y. Circulating platelet-neutrophil aggregates play a significant role in Kawasaki disease. *Circ J*. 2015;79:1349-1356.
59. Albensi BC. What is nuclear factor kappa B (NF-κB) doing in and to the mitochondrion? *Front Cell DevBiol*. 2019;7:154. doi:10.3389/fcell.2019.00154
60. Lawrence T. The nuclear factor NF-kB pathway in inflammation. *Cold Spring Harb Perspect Biol*. 2009;1:a001651. doi:10.1101/cshperspect
61. Philip S, Lee WC, Cherian KM, Wu MH, Lue HC. Role of antioxidants in horse serum-mediated Vasculitis in swine: potential relevance to early treatment in mitigation of coronary arteritis in Kawasaki disease. *Pediatr Neonatol*. 2017;58:328-337. doi:10.1016/j.pedneo.2016.07.007
62. Tandon VR, Verma S, Singh JB, Mahajan A. Role of antioxidants and oxidative stress in cardiovascular diseases. *J Hypertens*. 2005;7:61-63.
63. McCall TB, Boughton-Smith NK, Palmer RM, Whittle BJ, Moncada S. Synthesis of nitric oxide from L-arginine by neutrophils. Release and interaction with superoxide anion. *Biochem J*. 1989;261:293-296.
64. Mulligan MS, Moncada S, Ward PA. Protective effects of inhibitors of nitric oxide synthase in immune complex-induced vasculitis. *Br J Pharmacol*. 1992;107:1159-1162.

How to cite this article: Philip S, Jindal A, Krishna Kumar R. An update on understanding the pathophysiology in Kawasaki disease: Possible role of immune complexes in coronary artery lesion revisited. *Int J Rheum Dis*. 2023;00:1-11. doi:10.1111/1756-185X.14816