Autoimmune Aspects of Kawasaki Disease

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Abstract

Kawasaki disease (KD) is a vasculitis that is part of systemic vasculitis syndrome. It affects medium-sized vessels and is characterized by hypercytokinemia. Although the etiology of KD remains unidentified, epidemiological features point to the role of infection and genetic predisposition. Recent studies on KD revealed endothelial damage and resultant thrombin generation, as well as B-cell activation during the acute phase. Several antiendothelial cell autoantibodies (AECAs) have been identified in KD patients. Analysis of this phenomenon together with the recently developed concept of immunothrombosis reveals a potential pathogenic mechanism for KD. First, polyclonal antibodies generated against invading microorganisms would exhibit cross-reactivity toward endothelial cell components and become dominant during affinity maturation. Binding of AECAs to endothelial cells would cause endothelial activation or damage, with proinflammatory cytokine release, thus fostering a hypercoagulable state resulting from leukocyte activation by proinflammatory cytokines. This, in turn, would lead to coronary artery lesions. KD vasculitis might be initiated upon binding of AECAs to the vasa vasorum and progress to panvasculitis and a vulnerable vessel wall, resulting in an aneurysm. The aneurysm would cause flow recirculation and alteration of wall shear stress. Consequently, platelets activated by shear stress, along with ultralarge von Willebrand factor (VWF) released by endothelial cells, would cause platelet-driven arterial thrombosis. Autoimmunity-associated thrombosis initiated by binding of AECAs to endothelial cells might play a major role in the pathogenesis of certain subtypes of KD. The notion of KD consisting of subtypes, the major one of which is AECA-associated vasculitis, will help improve our understanding of KD and further promote early and accurate diagnosis, which remains challenging.

Key words: Autoimmunity. Coagulation. Endothelial damage. Inflammation. Immunothrombosis. Kawasaki disease.

Resumen

La enfermedad de Kawasaki (KD) se clasifica como una vasculitis de tamaño mediano enmarcada dentro del síndrome de las vasculitis sistémica caracterizadas por hipercitoquinemia. Aunque la etiología de KD permanece desconocida, sus características epidemiológicas apuntan al papel importante de la infección y la predisposición genética. Estudios recientes han descrito, durante la fase aguda de la enfermedad, la presencia de daño endotelial con generación de trombina, así como activación de células B. También se han identificado varios autoanticuerpos antiendoteliales (AECA) en estos enfermos. Todo ello, tomado en conjunto con el concepto recientemente desarrollado de inmunotrombosis, sugiere un nuevo mecanismo patogénico. Primeramente, algunos de los anticuerpos policlonales generados contra microorganismos invasores mostrarían reactividad cruzada hacia diversos componentes de las células endoteliales y se volverían dominantes durante el proceso de maduración de su afinidad. La unión de AECA a células endoteliales provocaría activación o daño endotelial, con liberación de citocinas proinflamatorias, fomentando consiguientemente un estado de hipercoagulabilidad por la activación de los leucocitos por estas citoquinas. Posteriormente, esta situación conduciría a lesiones en las arterias coronarias. La vasculitis KD podría iniciarse al unirse AECA a los vasa vasorum y progresar hacia una panvasculitis junto con una pared vascular vulnerable, lo cual daría lugar a la formación de aneurisma. El aneurisma provocaría una recirculación del flujo sanguíneo y una alteración de la pared vascular secundaria al estrés por cizallamiento. En consecuencia, las plaquetas activadas por este estrés de cizallamiento, junto con el factor von Willebrand (FVW) ultragrande liberado por las células endoteliales, causarían trombosis arterial. Esta trombosis asociada a autoinmunidad, iniciada por la unión de AECA a células endoteliales, podría jugar un papel importante en la patogénesis de ciertos subtipos de KD. La noción de KD como una enfermedad constituida por distintos subtipos, el principal de los cuales es vasculitis asociada a AECA, ayudará a facilitar una mejor comprensión de la misma y a promover aún más el diagnóstico precoz y preciso, lo que sigue siendo actualmente un reto importante para el clínico.

Palabras clave: Autoinmunidad. Coagulación. Daño endotelial. Inflamación. Inmunotrombosis. Enfermedad de Kawasaki.

Introduction

Kawasaki disease (KD) is an acute febrile illness that most frequently affects infants and children under 5 years of age. KD is also known as mucocutaneous lymph node syndrome, because it affects mainly the blood vessels, skin, mucous membranes, and lymph nodes. Acute systemic vasculitis in KD often progresses to coronary artery lesions (CALs), typically coronary aneurysms, which are the most serious complication of KD. However, coronary aneurysms rarely develop in children. KD has topped the list of acquired coronary diseases in children [1], despite the development of treatment with intravenous immunoglobulin (IVIG), which drastically reduces the incidence of coronary aneurysms. According to the latest report on the epidemiology of KD in Japan [2], cardiac lesions occur in 14.2% of patients (4.0% are noted on the first visit, 7.9% during the acute phase, and 2.3% as cardiac sequelae). IVIG reduces the KD-associated mortality rate to 0.01%. Among KD cases, 4.2% are recurrent and 2.1% are sibling cases. The incidence of KD has increased in recent years, and a nationwide survey revealed the highest ever rate in Japan (330.2/100 000 individuals in 2015).

Although half a century has passed since KD was first reported in 1967 [3] and a number of studies have explored the cause of this disease, its etiology remains unclear. This syndrome might consist of several subtypes of different etiologies. Recent progress in the field of immunology, especially the accumulation of findings on the interaction between immunity and coagulation, enables research into the pathogenesis of KD. In the current review, I attempt to summarize past and recent work on KD, including that of my colleagues and myself, by reconsidering the pathogenesis of KD in terms of the autoimmunity-inflammation-coagulation axis.

Pathophysiology

Systemic Vasculitis

The pathophysiological basis of KD involves systemic vasculitis affecting small- to medium-sized arteries in various organs, including the kidney, lung, and coronary arteries, with proinflammatory hypercytokinemia. KD vasculitis is considered to be a mixed-type vasculitis, with early and late lesions coexisting during an early stage of KD [4-7]. The recent and marked attention given to long-term sequelae of KD and the risk of acute coronary syndrome has led to the notion of subacute/chronic vasculitis of KD [8]. Subacute/chronic vasculitis might occur in some KD subtypes that follow a distinct disease course. Nevertheless, in most cases of KD, vasculitis is monophasic, ie, synchronized with a single peak in the inflammatory process [9,10]. The earliest pathological changes are observed 6-8 days after the onset of symptoms, starting with edema in the media and progressing to neutrophil and macrophage infiltration of the intima and adventitia. Inflammation then spreads, with panvasculitis across all layers of the vessel wall by day 10 [9]. However, the vessel size and layer in which inflammation starts at disease onset remain unclear [10]. According to previous studies, vessel inflammation in KD is initially confined to the capillaries and microvessels before subsequently expanding to medium-sized muscle arteries and veins [11]. On the other hand, some studies suggest that inflammation of medium-sized arteries is simultaneously elicited from the intima and adventitia [12].

Inflammation had long been considered to start in the luminal endothelium as a result of inflammatory cell infiltration (the "inside-out" concept) [13]. Nevertheless, recent studies revealed that the adventitia is the primary site of common acute vascular inflammation, supporting the so-called "outside-in" theory [14]. According to a study on atherosclerosis in humans, leukocyte adhesion molecules, such as vascular cell adhesion molecule 1, intercellular adhesion molecule 1, and E-selectin, are expressed on the intimal layer of vasa vasorum rather than on the arterial luminal endothelial cells [15]. This supports the "outside-in" theory and is consistent with the notion that the initial inflammation may begin in the vasa vasorum. In a recent study, *Candida albicans* water-soluble fraction was used to induce KD-like vasculitis in a mouse model [16]. The study revealed that the inflammation originates in the adventitia, with the vasa vasorum specifically serving as the initiator of vasculitis. These observations, well in agreement with the "outside-in" theory, suggest that KD vasculitis might initially occur in the vasa vasorum, subsequently affecting the adventitia and rapidly expanding to the entire vessel wall.

The Infectious Trigger Hypothesis

Three nationwide epidemics in Japan (in the years 1979, 1982, and 1986), regional aggregation and migration trends in epidemics, and the fact that infancy is the most likely period for onset of KD strongly suggest the involvement of an infectious factor in this disease [17,18]. The list of unsubstantiated etiologies proposed for KD includes bacteria, viruses (eg, Epstein-Bar virus, retroviruses, coronaviruses, and paramyxoviruses), and other microorganisms. Rowley et al [19] discussed the possibility of an as-yet-undefined ubiquitous agent entering the body through the respiratory route. Furthermore, the involvement of certain bacterial superantigens and those acting in cooperation with heat shock proteins produced by gut bacteria has been suggested [20-22]. Aside from these, a preformed toxin or environmental molecule related to *Candida* species was recently reported as the causative agent [23]. This finding is fascinating, because *Candida* has been linked to Kawasaki-like vasculitis in a mouse model. Nevertheless, the specific causative agent has yet to be identified, and none of the proposed etiological agents have been widely accepted.

On the other hand, the finding of pediatric patients whose parents have a history of KD and ethnic variation in morbidity suggest the involvement of host genetic factor(s). Parent-child cases and sibling cases indicate the involvement of both a host factor and an infectious one [17,18]. Susceptibility to KD has been linked to many immune-related gene variations [24]. Some of these (eg, *BLK* and *CD40*) are common susceptibility genes associated with autoimmune diseases, such as systemic lupus and rheumatoid arthritis, suggesting that KD shares a common pathophysiological mechanism with these autoimmune diseases [24]. Furthermore, unlike these common genes, *ITPKC* and *CASP3* variants are specific to KD disease. T-cell activation is strongly involved in endothelial cell damage by eliciting proinflammatory reactions, including the Ca^{2}+/nuclear

factor of activated T-cell (NFAT) signaling pathway at the onset of KD [25,26]. *ITPKC* negatively regulates T-cell activation, while *CASP3* is involved in the execution phase of apoptosis and also negatively regulates the Ca^2+/NFAT pathway [26]. Functional polymorphism of both genes would modulate T-cell regulation.

It was recently proposed that microorganisms play a role in KD disease, but only as a trigger of KD [27]. According to the infectious trigger hypothesis, viral and/or bacterial infection facilitates a cascade of events that leads to a magnified immunological response in genetically predisposed children. Multiple microorganisms would likely serve as the initial trigger. Following this scenario, Kusuda et al [28] and Hara et al [29] proposed that KD is an innate immune disorder resulting from the exposure of a genetically predisposed individual to microbe-associated molecular patterns in biofilms. However, in accordance with the infectious trigger hypothesis, cumulative findings, including those from my laboratory, enabled us to propose another, unique concept in the pathogenesis of KD. We have termed this concept autoimmunothrombosis.

Autoimmune Aspects of KD

B-Cell Activation

B cells are strongly involved in the pathogenesis of autoimmune diseases because of their ability to present antigens, produce cytokines, interact with T cells, and produce antibodies. Furthermore, the effectiveness of B-cell suppressive therapy for autoimmune diseases, ie, anti-CD20 antibodies [30], indicates the key role of B cells in both the pathogenesis and the treatment of autoimmune diseases. B cell–activating factor belonging to the tumor necrosis factor (TNF) family (BAFF), acts as a potent B-cell activator and plays a key role in the proliferation and differentiation of B cells; it is essential for the survival and differentiation of B cells and is associated with the disruption of peripheral immune tolerance [31,32]. BAFF levels are elevated in many autoimmune diseases [33].

In a previous study, my colleagues and I reported a marked elevation of BAFF levels in the acute phase of KD and their significant reduction after IVIG treatment [34]. These observations suggest activation of B cells in the acute phase and suppression of activated B cells by IVIG. Indeed, recent reports evidenced elevated levels of interleukin (IL) 17 in the acute phase of KD [35,36]. IL-17 induces a T_H17 cell-dependent inflammatory response, including antibody production [37]. In addition, IL-17 acts in concert with BAFF to directly enhance differentiation of B cells to immunoglobulin-secreting cells [38]. These findings indicate the possible involvement of B cells and an autoimmune mechanism in the pathogenesis of KD.

Since BAFF expression is induced by infection, eg, by respiratory syncytial virus [39], antecedent infection would induce BAFF expression before the onset of KD. In this process, the binding of BAFF to one of its cell surface receptors, BAFF-R, enhances B-cell survival [40]. In addition, NFAT activation leads to stimulation of the BAFF survival pathway [41]. It has been proposed that while *ITPKC* and *CASP3* gene products negatively regulate the Ca^2+/NFAT signaling pathway, dysfunctional variants might activate the BAFF survival pathway. Of note, IL-17 is mainly generated by activated T cells [42]. Since the *ITPKC* gene product negatively regulates T-cell activation, the presence of an *ITPKC* variant might lead to uncontrollable T-cell activation, which in turn might lead to elevated IL-17 levels. Ultimately, increased BAFF levels in conjunction with increased IL-17 levels in the acute phase of KD would enhance antibody generation. Collectively, in the acute phase of KD, antibody production would increase.

Antiendothelial Autoantibodies

In vasculitis syndrome, endothelial dysfunction resulting from vascular inflammation is critical for thrombus development. The primary role of endothelial cells is to maintain blood fluidity by controlling such biological events as coagulation, immune response, and inflammation. Various anticoagulants and antiplatelet mechanisms impact the function of endothelial cells to accomplish this control (Figure 1). Therefore, endothelial dysfunction may lead to thrombosis, and factors that cause endothelial dysfunction are important in KD vasculitis.

Antiendothelial autoantibodies (AECAs) are frequently detected in patients with vasculitis syndrome and well reflect the activity and severity of vasculitis. AECA binding might cause antibody-induced endothelial cell activation and damage [43] (Figure 2). The involvement of AECAs in the pathogenesis of KD has not yet been entirely proven, although it has been suspected for the last 3 decades [44,45]. As demonstrated in previous studies, sera from KD patients can lyse endothelial cells pretreated with proinflammatory cytokines [45-49]. The presence of AECAs in the serum of patients with KD has been demonstrated directly. Although the specific antigenic targets of AECAs in KD are unknown, the proposed targets, endothelial cell components, include tropomyosin, T-plastin, cardiac myosin, antioxidative peroxiredoxin 2, and 4-trimethylaminobutyraldehyde dehydrogenase [50-55]. Considering the remarkable structural and functional heterogeneity of endothelial cells [52], multiple target antigens may be recognized by AECAs in KD that are, at the same time, specific to proteins produced by the endothelium of vessels, ranging from small vessels, including the vasa vasorum, to medium-sized arteries.

Assessment of Endothelial Damage

Although endothelial dysfunction in patients with lifestyle-related disease or metabolic syndrome progresses steadily, AECA binding may acutely impair endothelial function. Regardless of the cause, endothelial dysfunction leads to repression or loss of anticoagulant and anti-inflammatory activity [57,58]. Therefore, assessment of endothelial damage is important, especially in KD with systemic vasculitis. Since direct observation of endothelial damage is not currently possible, endothelial dysfunction is assessed using laboratory tests. Commonly used endothelial damage markers include thrombomodulin (TM), antithrombin (AT), factor VIII activity (FVIII:C), and von Willebrand factor antigen (VWF:Ag).

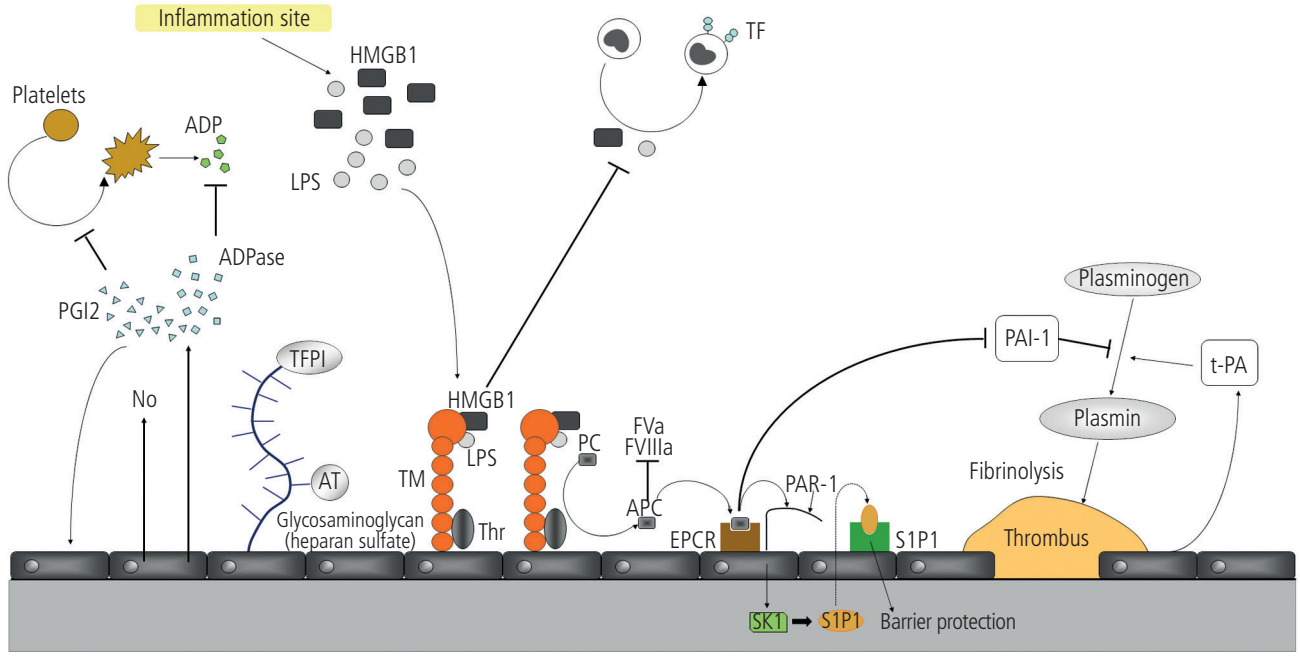

Figure 1. Anticoagulant and anti-inflammatory properties of endothelial cells. Prostaglandin I2 (PGI2) produced by endothelial cells inhibits platelet activation and induces generation of nitric oxide (NO) by endothelial cells. This leads to vessel dilatation. Ecto-ADPase released by endothelial cells also suppresses platelet function. The antithrombin action of antithrombin (AT) is enhanced by its binding to glycosaminoglycan. AT binds to thrombin (Thr), FIXa, and FXa, and inactivates them. Tissue factor pathway inhibitor (TFPI) bound to glycosaminoglycan inhibits the initiation phase of the extrinsic coagulation cascade by directly inhibiting FXa and the TF/FVIIa/FXa complex. Thrombomodulin (TM) expressed on the endothelial membrane forms a complex with thrombin, which decomposes and inactivates the high-mobility group box 1 protein (HMGB1), thereby preventing dissemination of inflammation via diffusion of HMGB1. TM also binds to lipopolysaccharide (LPS) and inactivates it. Thrombin binding to TM inhibits the procoagulant activity of thrombin. On the other hand, the ability of thrombin to activate protein C (PC) is greatly enhanced by thrombin binding to TM. Activated protein C (APC) inactivates coagulation factors FVa and FVIIIa and stimulates fibrinolysis by inhibiting plasminogen activator inhibitor 1 (PAI-1). APC exerts a protective effect on the endothelial barrier by binding to the endothelial protein C receptor (EPCR) and cleaving protease-activated receptor (PAR)-1, which activates sphingosine 1 phosphatase receptor 1 (S1P1) and leads to pleiotropic cytoprotective effects. Tissue plasminogen activator (t-PA) synthesized by the endothelium activates the fibrinolytic system. ADP indicates adenosine diphosphate; FVa, activated factor V; FVIIIa, activated factor VIII; S1P1, sphingosine 1 phosphatase receptor 1; SK1, sphingosine kinase 1; TF, tissue factor.

In a previous study of markers of endothelial damage in KD [59], my colleagues and I demonstrated that TM and AT levels are not elevated in the acute phase of KD. Thus, TM and AT levels cannot be used to adequately assess endothelial damage because of extravasation caused by enhanced vascular permeability [60,61] and because of increased renal excretion [62]. In fact, KD is often associated with hypoalbuminemia, which reflects increased renal excretion of albumin. The molecular mass of TM and AT is similar to that of albumin; consequently, these proteins would be excreted by the kidney in KD. By contrast, levels of both FVIII:C and VWF:Ag are significantly elevated in the acute phase. Unlike TM and AT, the molecular mass of FVIII and VWF released by damaged endothelial cells is high (in the circulating blood, FVIII molecules bind to VWF multimers, forming a complex of >20 000 kDa). VWF is the most important marker of endothelial damage [63], and FVIII is a sensitive indicator of endothelial damage [64]. Elevated VWF levels in the acute phase of KD reflect a prominent acute-phase reaction [65]. The proinflammatory cytokines IL-6, IL-8, and TNF-α can induce endothelial damage and further lead to the release of ultralarge VWF multimers (ULVWF) by endothelial cells [66,67]. ULVWF interact easily with platelets and may form a thrombus at the site of endothelial cell damage. In the clinical setting, VWF:Ag levels are elevated in various vasculitic disorders, as well as in sepsis [68]. In sepsis, impaired activity of VWF-cleaving protease, ADAMTS13, may contribute to the elevation of VWF:Ag levels by prolonging the half-life of VWF [69]. ADAMTS13 activity is reduced via several mechanisms under inflammatory conditions, ie, down-regulation of expression at the transcriptional level, proteolytic degradation, and consumption by high substrate levels [70]. According to Fujimura [71], enzyme-substrate imbalance between ADAMTS13 and VWF leads to the reduction of ADAMTS13 activity, and the resultant elevation of VWF levels culminates in a tendency toward thrombosis in KD with hypercytokinemia. Together with observations from my group, this suggests that reduction of ADAMTS13 activity might be associated with its consumption by the enormous amount of VWF, its substrate, which is released by damaged endothelium in systemic KD vasculitis.

Immunothrombosis

In addition to controlling life-threatening bleeding, the coagulation system may also act as a nonspecific biological

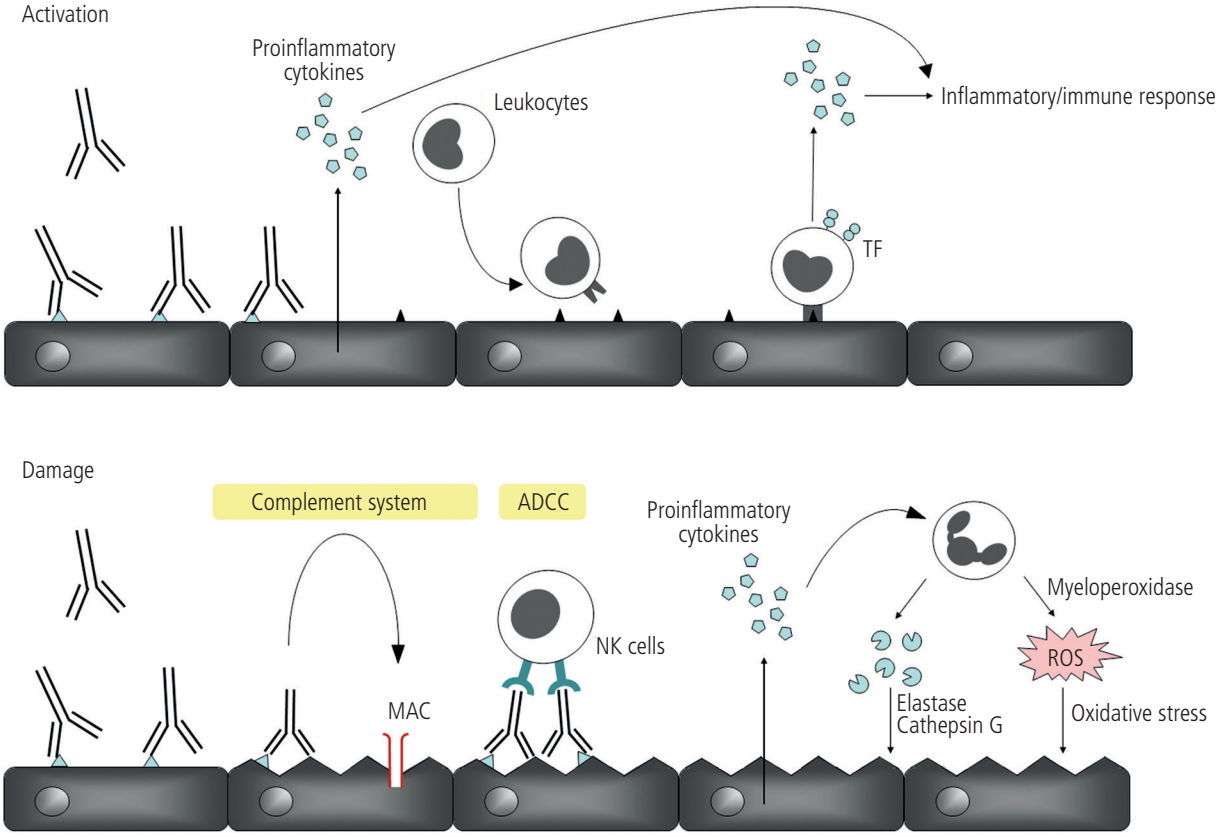

Figure 2. Endothelial activation and damage induced by antiendothelial cell autoantibodies (AECA). Activation of endothelial cells by AECA binding causes proinflammatory cytokine release and expression of adhesion molecules. Leukocytes adherent to endothelial cells express tissue factor (TF), which initiates extrinsic coagulation (upper panel). Endothelial damage is caused by AECA binding via complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC). The complement system has a final common pathway in which 5 proteins assemble into the membrane attack complex (MAC). The MAC inserts into cell membranes to form a functional pore, resulting in osmotic lysis. Upon AECA binding, endothelial cells release proinflammatory cytokines. Neutrophils activated by proinflammatory cytokines release proteases, such as elastase and cathepsin G. Furthermore, neutrophil myeloperoxidase generates reactive oxygen species (ROS), which cause further endothelial damage (lower panel).

defense mechanism against microbial invasion. The system is implemented to locally contain an invader: clotting occurs at the inflammation site to interrupt the blood flow, thereby preventing the dissemination of microorganisms in the body. Progress in immunology has revealed intimate tripartite interactions between innate immunity, inflammation, and coagulation, which has been further developed into a concept of immune-associated thrombosis or immunothrombosis [72,73]. The hemostatic cascade that closes an injured segment of a blood vessel is initiated by exposure of extravascular tissue factor (TF)–bearing cells after the vascular injury. By contrast, intravascular exposure of TF expressed on blood cells and endothelial cells via immunological responses fosters beneficial immune-associated thrombus formation locally in the vessel.

Pathogen invasion elicits the innate immune response. Myeloid-derived phagocytes, such as neutrophils and macrophages, recognize pathogen-associated molecular patterns through pattern-recognition receptors, including Toll-like receptors. Inflammatory transcription factors are then activated via intracellular signal transduction pathways, resulting in the release of proinflammatory cytokines [74]. These cytokines induce further production of proinflammatory cytokines through transforming growth factor beta-activated kinase (TAK) 1–mediated signal transduction and accelerate the acute inflammatory response. Upon stimulation by pathogen-associated molecular patterns, monocytes and monocyte microvesicles express TF [73]. Neutrophils activated by proinflammatory cytokines adhere to endothelial cells and express TF. Endothelial cells activated by the adhesion of neutrophils enhance the expression of TF. Various TF-expressing leukocytes bound to injured endothelial cells initiate extrinsic coagulation, with the endothelial cells acting as a scaffold of coagulation [75,76]. Such extrinsic coagulation produces a small amount of thrombin. In instances where abundant TF overcomes inhibition of tissue factor pathway inhibitor (TFPI) or TFPI function is impaired at the endothelial damage site, intrinsic coagulation progresses, with the resultant thrombin effectively activating platelets.

Together with activation of protease-activated receptor (PAR) 2 on the endothelial membrane, which leads to generation of proinflammatory cytokines [77], the mechanisms described cooperatively inhibit the pathogenic microorganism at the local level by interrupting the blood flow via formation of microthrombi, thus preventing systemic dissemination.

However, immunothrombosis might progress to a life-threatening thrombotic state if overwhelmed by systemic inflammation [75].

Autoimmunothrombosis in KD

In the acute phase of KD, the numbers of circulating polymorphonuclear neutrophils increase, with the cells becoming functionally activated. Neutrophilia with left shift is included in "Other significant clinical and laboratory findings" in the diagnostic guidelines for KD [78]. Mobilized and hyperactivated neutrophils lead to overproduction of neutrophil elastase and reactive oxygen species, both of which cause endothelial dysfunction. Moreover, the half-life of neutrophils is prolonged, because their apoptosis is inhibited during the acute phase of KD [79]. Nevertheless, since endothelial damage caused by elastase and reactive oxygen species is nonspecific, these factors alone cannot account for the confinement of KD arteritis mainly to small- to medium-sized arteries, especially the coronary artery. Importantly, the causes of the robust release of proinflammatory cytokines that leads to marked neutrophilia with left shift have not been extensively investigated.

As mentioned above, invasion of pathogenic microorganisms elicits a reaction of the innate immune system via pattern recognition receptors. Whilst these microorganisms are locally contained by immunothrombosis, humoral immunity is invoked consecutively, with specific antibodies against the pathogens produced 2-3 weeks after the infection is resolved. Some primary polyclonal antibodies might cross-react with endothelial antigens. In KD, a subclinical period occurs before manifestation of disease [6,7]. When cross-reacting antibodies become dominant during affinity maturation in that period, they serve as AECAs. The production of AECAs is further enhanced by elevated levels of BAFF and IL-17 in the acute phase of KD. When stimulation of AECAs is sufficiently high, AECA-bound endothelial cells intensely produce proinflammatory cytokines. After the release of proinflammatory cytokines, the same pathway for thrombus formation as in immunothrombosis is initiated, although the factors responsible for endothelial activation and/or damage are different and endothelial components recognized by AECAs might be unique to the vasa vasorum. In that case, proinflammatory cytokines and mediators produced by AECA-bound endothelial cells in the vasa vasorum would directly reach the adventitia, leading to inflammation and a hypercoagulable state.

Expression of TFs on AECA-bound endothelial membrane is associated with thrombosis in several clinical settings, such as preeclampsia, systemic sclerosis, and thrombotic thrombocytopenic purpura [80-82]. In KD, AECAs might specifically stimulate endothelial cells in vessels that range in size from the vasa vasorum to medium-sized vessels, resulting in local expression of TF. TF expressed on the endothelial membrane would then further accelerate intravascular extrinsic coagulation.

Serum levels of granulocyte-colony stimulating factor (G-CSF) are elevated in the acute phase of KD [83]. G-CSF is expressed constitutively by entities such as monocytes, macrophages, and endothelial cells. Its generation is enhanced by endotoxin and proinflammatory cytokines such as TNF-α and IL-6 upon infection [84]. G-CSF specifically and rapidly stimulates the production and activation of neutrophils. Hence, it may be that intense mobilization and activation of neutrophils initially occurs in the regions where the concentration of proinflammatory cytokines is high, that is, in the vicinity of AECA-bound endothelial cells. Enhanced expression of TF induced by the increasing number of activated neutrophils then initiates extrinsic coagulation. Oxidative stress associated with the activity of neutrophil myeloperoxidase and proteases, such as neutrophil elastase, might cause further cell and tissue damage in the vicinity of AECA-bound endothelial cells.

Reduction of TFPI activity because of its fragmentation by neutrophil elastase and cathepsin G hampers control of extrinsic coagulation in the acute phase of KD. Furthermore, neutrophil elastase and cathepsin G associated with neutrophil extracellular traps (NETs) suppress the anticoagulant system [85]. In addition, AECA binding impairs intrinsic anticoagulant activity as well as the fibrinolytic system, leading to endothelial damage. Proinflammatory cytokines released by endothelial cells inhibit the expression of coagulation-inhibiting proteins (eg, TM and endothelial protein C receptor) on the endothelium and increase the production of the antifibrinolytic agent plasminogen activator inhibitor 1 (PAI-1) [86].

High-mobility group box 1 (HMGB1) protein, an inflammatory mediator, is a key factor in dissemination of inflammation. HMGB1 is passively released from the nucleus of necrotic cells and potently activates nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) through Toll-like receptors 2 and 4, thus promoting the inflammatory response and cell migration [87]. HMGB1 is bound to TM in the endothelial membrane and is inactivated by the TM-thrombin complex. In the acute phase of KD, urinary TM levels (which reflect serum levels) are significantly higher than those in other pediatric diseases, such as IgA vasculitis, nephrotic syndrome, and bronchitis, and gradually decrease to within the normal range in the convalescent stage [88]. Since the assay used evaluates levels of soluble inactivated TM, elevated serum (urine) TM levels indicate cleavage and release of TM by endothelial cells. Hence, TM dysfunction occurs in KD with elevated TM levels and might primarily cause hypercoagulability associated with AECA-induced endothelial damage.

Endothelial damage also leads to the release of VWF. ULVWF molecules are released by the endothelium in KD, probably because of the reduced activity of ADAMTS13. ULVWF molecules are located on the surface of the damaged endothelium and mediate platelet adhesion by binding to platelet glycoprotein (GP) Ib [89-91]. Platelets activated by VWF binding further enhance coagulation by acting as a scaffold of intrinsic coagulation [75]. Since thrombocytosis is one of the most frequently observed clinical characteristics of KD, platelets might play a role in hypercoagulation in KD. Platelets might not only function as a scaffold of intrinsic coagulation but also self-aggregate and form thrombi in cooperation with ULVWF and fibrin produced by intrinsic coagulation. ULVWF molecules exhibit high thrombotic activity because of their high binding capacity for collagen and activated platelet receptors GPIb and GPIIb/IIIa. Thereby, they might easily cause platelet aggregation under high shear

conditions in the arterial system [92]. Activated platelets release P-selectin, which facilitates release of NETs [93]—composed of decondensed chromatin or histones released from the nucleus—and cell components [93]. Since histones can elicit platelet aggregability, platelet plugs may form, with NETs as scaffolding [94].

During AECA-dependent thrombosis (autoimmunothrombosis), endothelial damage caused by AECA binding initiates a sequence of events. First, proinflammatory cytokines are released by AECA-bound endothelial cells. Then, proinflammatory hypercytokinemia impairs endothelial cells and activates leukocytes, including neutrophils, monocytes, and macrophages. This leads to increased generation and activation of coagulation-related proteins and to suppression of anticoagulant proteins. Platelet activation follows, and a prothrombotic state is achieved. In fact, thrombotic tendency is well recognized in the acute phase of KD and is associated with disseminated intravascular coagulation in some cases of KD [95-98]. In a previous study, my colleagues and I reported that D-dimer levels exceeded the reference value in the acute phase of KD, thus indicating thrombin generation in that phase [59].

Further studies are warranted to identify the etiological agent of the antecedent infection, antibodies that cross-react with endothelial cellular component, and their epitopes. However, published reports indicate the possible involvement of a multiplicity of pathogenic microorganisms, antigenic endothelial component proteins, and their epitopes. Elucidation of the underlying pathophysiological mechanisms and undertaking measures for treatment based on these mechanisms are more important than identifying the cause.

Treatment From the Perspective of the Autoimmunity-Inflammation-Coagulation Axis

The mainstay of treatment for KD is IVIG, preferably given within 10 days of the onset of fever. IVIG is effective for various diseases, suggesting complicated and wide-ranging mechanisms that underpin this treatment [99]. These mechanisms include blockade of immunoglobulin Fc receptors of the reticuloendothelial system (especially FcγRIIIA), an anti-inflammatory effect achieved by suppression of proinflammatory cytokines, neutralization of autoantibodies by anti-idiotype antibodies contained in therapeutic immunoglobulin preparations, and down-regulation of B and T cells and BAFF [34,100-102]. Consequently, IVIG exerts anti-inflammatory effects, aids preservation of endothelial cells, inhibits autoantibody production, and neutralizes and clears autoantibodies. Previous observations that IVIG, instead of antiplatelet aspirin intake, prevents severe CALs [103,104] suggest that molecules other than those related to platelet activation constitute the pathophysiological basis of vascular lesions, ie, autoantibodies. Whereas the mechanisms of action of IVIG in KD are conceived mainly for suppression of endothelial activation and proinflammatory cytokines [105], little attention has been paid to the effect of IVIG on AECAs. IVIG would be able to reduce endothelial damage by neutralizing AECA (by anti-idiotype antibodies) and/or inhibiting AECA production. Therefore, it seems reasonable to use IVIG for treating AECA-associated KD vasculitis.

Aspirin is usually given because of its anti-inflammatory and antiplatelet properties. High- or medium-dose aspirin is administered in the acute phase, and low-dose aspirin after defervescence. Since KD is characterized by enhanced platelet aggregability, 6-8 weeks of low-dose aspirin therapy is recommended [106]. Considering that platelet activation is essential as a scaffold of intrinsic coagulation and that binding of VWF to platelets is critical for platelet adhesion and aggregation [107], inhibition of platelet activation by oral aspirin intake for the control of KD vasculitis is pathophysiologically rational. Indeed, fever subsides within 24-48 hours in most KD patients after successful IVIG and oral aspirin intake.

Nevertheless, 15%-25% of KD patients are refractory to initial IVIG treatment combined with aspirin intake. Since the incidence of IVIG failure and that of CALs are very similar, IVIG-refractory patients may experience CAL-related complications. Choosing the treatment for IVIG-refractory patients remains a major challenge. Treatment of such patients in Japan involves additional IVIG, corticosteroids, neutrophil elastase inhibitor (urinastatin), and plasmapheresis [106]. Furthermore, the effectiveness of cyclosporin (immunosuppressant with specific activity against T lymphocytes) and infliximab (TNF-α inhibitor) has been reported [108,109], although both approaches are still being developed.

Rituximab, a genetically engineered chimeric anti-CD20 monoclonal antibody, is used in antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis. If KD is categorized as autoimmune-mediated vasculitis, ie, AECA-associated vasculitis, B cell–targeted therapy may offer rational alternatives [110]. A single case report on the effectiveness of anti-CD20 monoclonal antibody for IVIG-refractory KD [111] supports this notion. Furthermore, inhibition of BAFF and IL-17 might constitute a therapeutic target for suppression of AECA production in KD, as in autoimmune diseases [112-114]. Further studies are warranted to confirm the efficacy of these agents.

The abovementioned agents, except for antiplatelet aspirin, effectively suppress autoantibody generation upstream of a pathological pathway. It should be feasible to devise strategies to block the downstream events that are directly responsible for the prothrombotic event. To achieve this, TM may be a potential target for the treatment of KD. Since TM shows a superior anticoagulant activity, which is incomparable with that of the existing protease inhibitors, recombinant human TM has been widely used for sepsis-associated disseminated intravascular coagulation in Japan, and its effectiveness has been substantiated by clinical observation [115]. Since coagulopathy is associated with endothelial damage in both septic disseminated intravascular coagulation and KD, replenishment of innate TM with recombinant TM may constitute a treatment option in KD with a prominent hypercoagulable state. Further studies should pave the way toward therapeutic use of recombinant TM for KD in the future.

Future Considerations and Conclusions

Also known as mucocutaneous lymph node syndrome, KD is a condition that might be difficult to explain from the standpoint of a single pathogenic mechanism. However, accumulated evidence strongly suggests the involvement of an autoimmune mechanism in the pathogenesis of KD, at least in some subtypes of KD. AECAs developed in response to an antecedent infection might play a key role in the process. Neutrophilia, a hypercoagulable state, and the ensuing CAL might be triggered by AECA-bound endothelial activation and injury. Nevertheless, the pathogenetic mechanisms of KD will not necessarily be confined to AECA-associated vasculitis.

One of the biggest challenges remaining in the treatment of KD is the difficulty in diagnosis, especially in incomplete forms of KD, which may be associated with serious CAL; this is because diagnosis is based on a set of criteria that are entirely clinical, and laboratory tests rarely provide conclusive evidence [116]. Another challenge is determining whether KD vasculitis is self-limiting or persistent with or without exacerbations and remissions such as subacute/chronic vasculitis of KD. However, these become more understandable when KD is considered to consist of subtypes. Information from evolving genome-wide association studies and epigenome-wide association studies, as well as multiomics technologies [117], might be utilized for the classification of KD subtypes. With the understanding that KD consists of subtypes, the main one of which might be AECA-associated vasculitis, I expect that further elucidation of the mechanisms of pathogenesis and the pathological conditions of each subtype of KD will yield critical insights into KD that will help facilitate the early diagnosis of subtypes and the implementation of personalized approaches to treatment.

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Conflicts of Interest

The author has no conflicts of interest to declare.

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