**Review Article**

# Pathogens in Vasculitis: Is It Really Idiopathic?

Chie Miyabe[1], Yoshishige Miyabe[2], Ryujin Miyata[1], and Naoko Ishiguro[1]

**Abstract:**
Vasculitis is an autoimmune disease characterized by the infiltration of leukocytes in blood vessels.
An increasing number of studies on human and animal models have implicated various microorganisms in the pathogenesis of vasculitis. Previous studies have shown the presence of infectious agents, including viruses, bacteria, and fungi, in diseased vessels. However, despite continued research, the link between infection and vasculitis is not fully understood, possibly owing to the lack of appropriate animal models that mirror human disease and the technical limitations of pathogen detection in blood vessels. Among the pathogen-induced animal models, *Candida albicans* water-soluble fraction (CAWS)-induced coronary arteritis is currently considered one of the representative models of Kawasaki (KD) disease. Advances in metagenomic next-generation sequencing have enabled the detection of all nucleic acids in tissue, which can help identify candidate pathogens, including previously unidentified viruses. In this review, we discuss the findings from reports on pathogen-associated vasculitis in animal models and humans, with a specific focus on the investigation of the pathogenesis of vasculitis. Further studies on animal models and microbes in diseased vessels may provide important insights into the pathogenesis of vasculitis, which is often considered an idiopathic disease.

**Key Words:**
vasculitis, infection, pathogen, animal models

## 1. Introduction

Vasculitis is an autoimmune disorder characterized by the presence of inflammatory leukocytes in blood vessels with destructive damage caused to the mural structures. The nomenclature and definition of vasculitis were first proposed at the International Chapel Hill Consensus Conference held in 1994 and updated in 2012 to incorporate advances based on recent developments in medical expertise [1]. Vasculitis is categorized by size, type, and location according to the type of affected vessels: (i) small vessels, e.g., ANCA-associated and immunoglobulin A (IgA) vasculitis; (ii) medium vessels, e.g., polyarteritis nodosa (PAN) and Kawasaki disease (KD); and (iii) large vessels, e.g., Takayasu arteritis (TA) and giant cell arteritis (GCA) [1].

The etiology of vasculitis remains poorly understood, and multiple vasculitis-related syndromes are considered idiopathic. For instance, it is estimated that 45%-55% of cutaneous vasculitis cases is idiopathic, 15%-20% is caused by infections, 15%-20% is secondary to inflammatory diseases, 10%-15% is drug-induced, and less than 5% is associated with malignancy [2]. However, an increasing number of human and animal studies suggest that vasculitis is not only caused by a few infectious agents but also, in fact, associated with various pathogenic agents, including viruses, bacteria, fungi, and parasites. The coronavirus disease 2019 (COVID-19) epidemic has attracted an unanticipated interest in infection-associated inflammatory autoimmune diseases, including vasculitis. During the pandemic, children were reported to develop vasculitis-like inflammatory symptoms with clinical features similar to those of KD. This condition was described as multisystem inflammatory syndrome in children (MIS-C) and has been associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure [3]. Comparable to other autoimmune conditions, an aberrantly activated host immune response to the pathogen is considered to play a central role in vasculitis.

In this review, we summarize previous reports on animal vasculitis models and human vasculitis cases associated with infectious agents and discuss the potential approach for investigating the pathogenesis of vasculitis, which is often considered an idiopathic disease.

[1] Department of Dermatology, Tokyo Women's Medical University, Tokyo, Japan. [2] Department of Cell Biology, Institute for Advanced Medical Sciences, Nippon Medical School, Tokyo, Japan
Corresponding author: Chie Miyabe, cmderma.ak@twmu.ac.jp

**Table 1.** Animal Models of Pathogen-Associated Vasculitis.

| | | | |
|---|---|---|---|
| **Viruses** | PRRSV | Pig | Aorta, renal arteries, postcapillary venules in the dermis |
| | Aleutian mink disease virus | Mink | Necrotizing arteritis of small muscular arteries |
| | Equine arteritis virus | Equine | Small-vessel vasculitis throughout the body |
| | Newcastle disease virus | Chicken | Cerebral vasculitis |
| | Lymphocytic choriomeningitis virus | Mouse, hamster | Glomerulonephritis and widespread vasculitis |
| | Cytomegalovirus | Mouse | Aortitis and pulmonary arteritis |
| **Bacteria** | *Chlamydia pneumoniae* | Rabbit | Aortitis |
| | *Borrelia burgdorferi* | Rat, mouse | Arthritis, myocarditis, and vasculitis (model of Lyme disease) |
| | BCG + *Mycobacterium intracellulare* | Mouse | Coronary arteritis |
| | *Mycoplasma gallisepticum* | Turkey | Cerebral arteritis |
| | *Lactobacillus casei* | Mouse | Coronary arteritis |
| **Fungi** | *Candida albicans* | Mouse | Coronary arteritis |
| | *Candida krusei* | Mouse | Coronary arteritis |

PRRSV, porcine reproductive and respiratory syndrome virus; BCG, Bacillus Calmette-Guérin

## 2. Animal Models of Pathogen-Associated Vasculitis

Animal models are useful tools for improving our understanding of the pathways and molecules that might be involved in disease induction. Compared with models of other autoimmune disorders, such as multiple sclerosis and rheumatoid arthritis, the animal models of vasculitis are less frequently studied. Notably, among the multiple experimental models of vasculitis that have been developed, several are induced by pathogens, including viruses, bacteria, and fungi (**Table 1**). For example, the injection of a *Candida albicans* water-soluble fraction (CAWS) in mice led to the inflammation of the aortic root and coronary arteries. This can be used as an appropriate model for KD [4]. A deeper understanding of the mechanism by which pathogens induce vasculitis could help develop novel therapeutic targets and prevention strategies for vasculitis. In this section, an overview of previously reported animal models of vasculitis induced by pathogens has been provided.

### 2.1 Viruses
Numerous animal models of vasculitis associated with viral infection have been studied, mostly in the 1970s-2000s. For instance, porcine reproductive and respiratory syndrome virus (PRRSV) induces systemic necrotizing vasculitis involving the skin and kidneys in pigs [5]. This phenomenon was observed during studies on the porcine disease that spread across Europe and North America in the 1990s.

PRRSV antigens were detected by immunohistochemistry in macrophages surrounding the blood vessels in the skin and kidneys. Aleutian mink disease, caused by the Aleutian disease virus, is a persistent viral infection of minks characterized by prolonged clinical course, progressive weight loss, splenomegaly, lymphadenopathy, hepatomegaly, glomerulonephritis, and necrotizing arteritis [6]. The formation of arterial lesions could be prevented by immunosuppressive therapy. The percentage of minks with arterial disease following experimental infection varied from 19% to 40%. Immunoglobulin G (IgG), complement component 3 (C3), and, occasionally, viral antigens are deposited in the affected glomerular capillaries, suggesting that the deposition of antigen-antibody complexes is the causal factor of arteritis [7]. Equine arteritis virus (EAV), the causative agent of equine viral arteritis, is a small, single-stranded RNA virus related to coronaviruses and toroviruses [8]. EAV-infected horses develop rapid-onset fever, depression, leukopenia, and necrotizing arteritis. Adult horses generally make an uneventful recovery after a viremic phase that may persist for up to 40 days after infection. Chickens infected with the Newcastle disease virus develop pneumonitis followed by severe encephalitis. Histologically, encephalitis is characterized by neuronal degeneration and proliferative vasculitis in the cerebellum, and viral antigens in the neurons, glial cells, and endothelial cells are detected [9]. Mice congenitally or neonatally infected with lymphocytic choriomeningitis virus (LCV) develop gromerulonephritis and necrotizing vasculitis of small- and medium-sized arteries, especially in the kidneys and spleen [10]. Hamsters with persistently high levels of LCV viremia develop chronic glomerulonephritis and widespread vasculitis, whereas hamsters with cleared infection do not develop lesions [11]. Murine cytomegalovirus (MCMV)-infected mice showed a high prevalence of arteritis in both the aorta and pulmonary arteries, with mononuclear cell infiltrates de-

tected in the intima and adventitia [12]. The distribution of the cellular infiltrate affects the adventitial surface more severely. Lymphocytes predominantly infiltrate the adventitia, whereas fewer lymphocytes and more macrophages are detected in the medial and intimal infiltrates. MCMV antigens have also been detected in the walls of affected blood vessels.

## 2.2 Bacteria

*Chlamydia pneumoniae* is a common human respiratory pathogen that has also been associated with atherosclerosis. New Zealand white rabbits intranasally inoculated with *C. pneumoniae* showed inflammatory changes in the aorta [13]. Immunohistochemical analysis with an anti-*Chlamydia* antibody yielded positive results in some aortic endothelial cells [14].

Borrelia burgdorferi is primarily responsible for human Lyme borreliosis. LEW/N rats intraperitoneally inoculated with *B. burgdorferi* developed Lyme disease-like symptoms, such as arthritis, tendonitis, bursitis, myocarditis, and aortitis [15]. In the early stage of the disease, *B. burgdorferi* was detected in the endothelium in the periarticular connective tissues, synovium, and tendons. In the late stage, the titer of IgG antibodies against *Borrelia* antigens increased with time, indicating the continued antigenic stimulation from persistent *Borrelia* infection. Accordingly, systemic inflammation symptoms, including vasculitis, appeared to be secondary to *Borrelia* infection in the tissues and immune response to the same. In the mouse model of Lyme borreliosis (in C3H/He mice), vasculitis of medium and large arteries in cardiac and knee lesions was observed [16]. Mice inoculated with Bacillus Calmette-Guérin followed by booster immunizations with *Mycobacterium intracellulare* developed coronary arteritis [17]. In another study, turkeys were intravenously injected with various doses of *Mycoplasma gallisepticum*, the causative agent of chronic respiratory disease in birds [18]. The arteries of the brain were primarily affected among those in multiple organs, including the heart, liver, lung, spleen, kidney, and gastrointestinal tract. It was demonstrated that viable *Mycoplasma* can induce arteritis. In addition, the protective effect of the lesions was observed by the administration of tetracycline and gold thiomalate. The intraperitoneal injection of nonviable *Lactobacillus casei* cell-wall extract (LCWE) induced coronary arteritis in mice [19]. Arteritis is accompanied by the disruption of the arterial intima and media with the formation of aneurysm, the hallmark of KD in children. This unique mouse model was dependent on the signaling of TLR2 and MyD88 and the subsequent release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF [20].

## 2.3 Fungi

Over the last few decades, several murine models of KD have been developed, including the CAWS- and LCWE-induced vasculitis models, which share pathological features with the human disease. Previous studies have suggested that exposure to wind-borne *Candida* might trigger KD [21]. CAWS is a mannoprotein-β-glucan complex secreted by *C. albicans* that induces cardiac arteritis resembling the symptoms of human KD when intraperitoneally injected into mice. CAWS is noninfectious since it does not contain live fungal cells, and it is considered a pathogen-associated molecular pattern (PAMP) that activates the innate immune response. CAWS-induced coronary arteritis is widely used and considered an appropriate model for studies on the pathogenesis of arteritis and for developing novel treatments [22], [23]. We have previously shown that the dectin-2-mediated induction of CCL2 production by resident macrophages initiates vascular inflammation followed by IL-1β secretion in a dectin-2/Syk/NLRP3 inflammasome-dependent pathway [4].

# 3. Pathogen-Associated Vasculitis in Humans

Various pathogens are reported to induce vasculitis in humans. Viruses are primarily associated with small-vessel vasculitis, whereas bacterial infections affect vessels of all sizes, including the aorta [24]. Fungal infection is usually associated with large-vessel vasculitis. In this section, we classify pathogen-associated vasculitis in humans based on the type of microorganism (**Table 2**), including SARS-CoV-2, reported in previous and recent studies.

## 3.1 Viruses

The viruses associated with human vasculitis are surprisingly diverse. Hepatitis B virus (HBV) is associated with two types of vasculitis: cryoglobulinemic small-vessel vasculitis and PAN. Immune complex (IC)-mediated small-vessel vasculitis is reported in approximately 10% of patients with HBV infection [25]. The association between PAN and HBV has been frequently reported (10%-54%), usually within the first 6 months of HBV infection [26]. The detection of the hepatitis B surface antigen in the vessel wall has been reported in approximately 30% of patients with systemic vasculitis and in up to 50% of patients with PAN [27]. Clinical HBV-associated PAN is barely distinguishable from classic PAN; however, relapses are considerably rare [28]. Chronic hepatitis C virus (HCV) infection can manifest as mixed cryoglobulinemia (MC), which has been detected in over 50% of patients with HCV infection. Approximately 5% of patients with HCV-associated MC develop cryoglobulinemic vasculitis, owing to circulating IC deposition in small vessels [29], [30]. Several types of vasculitis are associated with HIV infection. Systemic necrotizing vasculitis, leukocytoclastic vasculitis, cryoglobulinemia, central nervous system (CNS) vasculitis, and PAN have been reported [31]. PAN in patients with HIV affects the neuromuscular system and skin more frequently than other organs. HIV antigens and particles are detectable in the vessels in such patients [32]. Virus replication with a direct injury of the vessel wall or IC deposition in the vessel wall is presumed. Varicella-zoster virus

**Table 2.** Human Vasculitis Associated with Pathogen.

| | | |
|---|---|---|
| **Viruses** | HBV | PAN, cryoglobulinemic vasculitis |
| | HCV | Cryoglobulinemic vasculitis |
| | HIV | Large-, medium-, and/or small-sized vessel vasculitis, cerebral vasculitis, cryoglobulinemic vasculitis |
| | VZV | Small- and large-vessel vasculitis of the cerebrum, retina, choroid, kidneys, and skin |
| | Cytomegalovirus | Vasculitis of the gastrointestinal tract, central nervous system, retina, and cutaneous tissue |
| | HTLV-1 | Necrotizing retinitis, cutaneous vasculitis |
| | EBV | Leukocytoclastic vasculitis, granulomatous vasculitis, large-vessel vasculitis |
| | Parvovirus B19 | IgA vasculitis, PAN, Kawasaki disease, Wegener's granulomatosis, GCA, cryoglobulinemic vasculitis |
| | Hantavirus | Cutaneous vasculitis |
| | Herpes simplex virus | Necrotizing vasculitis of small- and medium-sized lung and peripancreatic arteries |
| | Rubella virus | Cutaneous vasculitis |
| | Coronavirus | Kawasaki disease, MIS-C |
| **Bacteria** | *Staphylococcus aureus* | Aortitis, GPA, Kawasaki disease |
| | *Streptococcus species* | IgA vasculitis, PAN, KD |
| | *Bartonella henselae* | Small-vessel vasculitis, endocarditis |
| | *Mycobacterium tuberculosis* | Takayasu arteritis; IgA vasculitis; cerebral, cutaneous, and retinal vasculitis |
| | *Salmonella* | Aortitis |
| | *Clostridium* | Aortitis |
| | *Burkholderia* | GCA |
| | *Mycoplasma* | IgA vasculitis, cerebral vasculitis, KD |
| **Fungi** | *Aspergillus* | Cerebral vasculitis, endocarditis |
| | *Coccidioides* | Cerebral vasculitis, endocarditis |
| | *Candida species* | Cutaneous small-vessel vasculitis, cerebral vasculitis, endocarditis |
| **Others** | *Treponema pallidum* | Aortitis, retinal vasculitis, cutaneous small-vessel vasculitis |
| | *Orientia tsutsugamushi* | Systemic vasculitis |
| | *Borrelia burgdorferi* | Cerebral and retinal vasculitis, GCA |

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; VZV, varicella-zoster virus; HTLV-1, human T-cell leukemia virus type 1; EBV, Epstein-Barr virus; PAN, polyarteritis nodosa; GPA, granulomatosis with polyangitis; GCA, giant cell arteritis; MIS-C, multisystem inflammatory syndrome in children

has been associated with GCA and vasculitis that affects the CNS, retinal and choroidal small vessels, skin, and kidney [25], [33]. Cytomegalovirus (CMV) infection can lead to vasculitis in various organs associated with the gastrointestinal tract, CNS, retina, and cutaneous tissue [25]. As CMV is detected in 50%-55% of healthy vessels [34], whether it is the causative agent of vasculitis or simply a less harmful commensal is unclear. Human T-cell lymphotropic virus type 1 (HTLV-1) infection causes adult T-cell leukemia, an aggressive malignancy of CD4-positive lymphocytes. HTLV-1-associated uveitis is a common ophthalmic manifestation of this viral infection;

however, retinal vasculitis has also been reported [35]. HTLV-1-associated cutaneous lymphocytic vasculitis, in which malignant T cells infiltrate the skin, has also been reported [36]. Epstein-Barr virus (EBV), which causes various human B-cell lymphomas and infects B cells, has been implicated in the pathogenesis of leukocytoclastic and granulomatous vasculitis, as well as in vasculitis characterized by widespread large-vessel and coronary artery aneurysms [37]. It is also associated with KD [38]. Various autoimmune diseases, including juvenile idiopathic arthritis, systemic lupus erythematosus, systemic sclerosis, reactive arthritis, Sjogren's syndrome, polymyositis,

dermatomyositis, and vasculitis, have been associated with parvovirus B19 infection [39]. The association between parvovirus B19 infection and vasculitis has been reported in Henoch-Schönlein purpura, PAN, KD, Wegener's granulomatosis, GCA, and cryoglobulinemic vasculitis[25], [39], [40]. Parvovirus B19-associated vasculitis is considered to result from direct injuries in the infected vessel wall. Acute hantavirus infection has been associated with cutaneous vasculitis [41]. Necrotizing vasculitis of small- and medium-sized lung and peripancreatic arteries was observed in a neonatal patient with herpes simplex infection [42]. An infant with congenital rubella syndrome showed cutaneous vasculitis [43].

The association between New Haven coronavirus and KD has been reported in studies since the 1970s [44], [45]. However, these findings received limited attention until the recent COVID-19 outbreak. In the early stages of the COVID-19 outbreak, pediatricians reported MIS-C, which has features similar to those of KD and toxic shock syndrome [46]. Compared to that in severe COVID-19, the polymerase chain reaction (PCR) cycle thresholds for SARS-CoV-2 were higher in MIS-C, indicating a reduced viral burden and validating the concept that MIS-C can occur in response to an infection [47]. Notably, patients with MIS-C not only exhibited appropriate antibody responses to SARS-CoV-2 but also produced autoantibodies specific for endothelial, gastrointestinal, and immune-cell antigens [48].

Overall, a wide variety of viruses have been implicated in vasculitis by different mechanisms. For example, direct endothelial cell invasion can be undertaken by various viruses, such as HBV, HIV, CMV, and parvovirus B19. IC deposition in the vessel wall and subsequent complement activation and immune-cell recruitment are important processes in cryoglobulinemic vasculitis in HCV-associated vasculitis. In addition, the invasion of malignant CD4-positive lymphocytes infected with HTLV-1 can also lead to vasculitis. However, it should be noted that only a limited number of viruses have been identified using traditional techniques such as enzyme-linked immunosorbent assay, immunohistochemistry, or PCR, which constitute ~0.07% of all viral entities [49]. In other words, at this point, the chances of identifying more unknown pathogenic viruses in the vessels cannot be ruled out.

### 3.2 Bacteria

The incidence of vasculitis induced by bacterial infection is assumed to have decreased from that reported half a century ago. Vasculitis associated with *Staphylococcus aureus* infection is usually a complication resulting from bacterial dissemination and direct invasion of the damaged vessel wall with the formation of a "mycotic aneurysm," which is most commonly detected in the aorta [25]. In granulomatosis with polyangiitis, the chronic nasal carriage of *S. aureus* is linked to disease activity and relapses that can be reduced with antibacterial treatment [50]. Staphylococcal infection triggers the release of proteinase 3 and reactive oxygen species from neutrophils, and superantigens, such as staphylococcal protein A, trigger the activation of auto-specific T and B cells [51]. The metagenomic analysis of intestinal microbiota suggested that the number of sequencing reads with similarity to *Streptococcus* species markedly increased during the acute phase in patients with KD [52]. The correlation between *Streptococcus* infection and IgA vasculitis is widely acknowledged [53]. Streptococcal antigens, such as nephritis-associated plasmin receptor and IgA-binding M proteins, have been identified in the kidneys of patients with IgA vasculitis. *Streptococcus* species have also been associated with PAN and KD [24], [26]. *Bartonella henselae* is the primary causative agent of cat scratch disease, which presents with suppurative lymphadenopathy. It has also been associated with glomerulonephritis, small-vessel vasculitis, and endocarditis in immunocompromised patients [54]. TA has been linked to *Mycobacterium tuberculosis* infection, perhaps via cross-reactivity against vascular peptides that mimic the antigens of *M. tuberculosis*. *IS6110* and *HupB* sequences, which are typically used to identify *M. tuberculosis*, were detected in 82% of tissue samples collected from patients with tuberculosis, 70% of samples from patients with TA, and 32% of samples from patients with atherosclerosis [55]. IgA vasculitis [56] and cerebral [57], cutaneous [58], and retinal vasculitis [59] have also been associated with *M. tuberculosis* infection. *Salmonella* aortitis is a known complication of *Salmonella* infection that typically affects the abdominal aorta and requires surgical intervention [60]. *Clostridium septicum* arteritis is also a rare life-threatening arterial infection often associated with gastrointestinal or hematological malignancy [61]. Koening et al. showed that a *Burkholderia*-like strain is the causative agent of GCA [62]. This was the first report to directly demonstrate the effects of bacterial infection in vasculitis; however, further studies need to confirm the findings. Infection with *M. pneumoniae* has been associated with Henoch-Schönlein purpura (now referred to as IgA vasculitis), CNS vasculopathy, and KD [30].

### 3.3 Fungi

Although large-vessel vasculitis caused by fungal infection has rarely been reported in recent years, it was previously reported in immunocompromised patients or as a complication in cardiovascular surgery [24]. Most cases involved endocarditis; however, several cases of invasive fungal vasculitis or meningitis, primarily caused by *Aspergillus* and *Coccidioides*, have also been reported [63], [64]. These fungi invade vessels and cause thrombosis and infarction.

In contrast to findings from animal models, the association between *Candida* infection and coronary arteritis has not been confirmed in humans. However, invasive *Candida* infection causes cutaneous leukocytoclastic vasculitis, owing to the invasion of the blood vessels by pseudohyphae [65]. *Candida* endocarditis and meningitis have also been reported [66], [67].

### 3.4 Other pathogens

Cardiovascular involvement reported later in the course of un-

treated syphilis, such as aortitis of ascending aorta, has been estimated to occur in 10% of untreated syphilis cases [68]. Retinal and cutaneous small-vessel vasculitis have also been reported [69]. Scrub typhus, a disease caused by mite-borne rickettsia, is an acute febrile disease caused by *Orientia tsutsugamushi*. Since the vascular endothelium is the principal target site of the organism, it is considered to affect nearly every organ system, leading to varied clinical manifestations [70]. Lyme disease, a common tick-borne infection in the northern hemisphere, is caused by *B. burgdorferi*. CNS involvement, primarily represented by neuroborreliosis, is characterized by perivascular and vascular lymphocytic infiltration associated with the presence of *B. burgdorferi* DNA [71]. Retinal vasculitis has also been reported [72]. A case report on GCA, in which spirochetes compatible with *Borrelia* species were identified in temporal artery biopsy specimens and blood culture samples, has also been published [73].

## 4. Discussion

The COVID-19 pandemic that started in December 2019 notified that the greatest threat to humanity is still infectious diseases in the modern era. Infections can trigger autoimmune diseases, including vasculitis, in genetically susceptible individuals by modulating host immune responses.

Animal models of vasculitis provide valuable information that can help elucidate the mechanism underlying the pathogenesis of vasculitis. These models have also helped identify novel therapeutic targets. Multiple theories have been proposed to explain how infections induce autoimmune diseases; the potential mechanisms include bystander activation, pathogen-induced necroptosis, superantigen cross-linking, and molecular mimicry [74]. In the human and animal models of pathogen-induced vasculitis, although direct infection of endothelial cells by pathogens has been observed in multiple cases, the exact mechanism remains not completely understood. Most animal models, especially of virus- or bacteria-induced vasculitis, were actively studied until the 1990s. However, the models have been less frequently studied in the last two decades. The challenges in handling larger experimental animals and harmful pathogens, inconsistency with the human disease, and potential ethical issues could be some of the reasons for this. Alternatively, animal models of LCWE- or CAWS-induced KD have been extensively studied in the last two decades. A common characteristic of these models is that neither LCWE nor CAWS is inherently infectious and are only the cell-wall extracts of *Lactobacillus casei* and *C. albicans*, respectively. Therefore, these agents are considered superantigens or PAMPs. The advantages of these models include high reproducibility and similarity to human KD, owing to which these can be used to assess novel therapeutic interventions for KD. However, an important caveat is that neither of the two bacteria has been identified in human KD, which may occasionally give rise to concerns that the models do not faithfully repre-

sent human KD. Ideally, animal models of diseases should mirror the pathogenesis and mechanism of human diseases. Although these animal models are not identical to human vasculitis, they remain useful as long as the differences are known and the results are carefully interpreted. Indeed, studies on the animal models of KD have led to the discovery of the essential role of IL-1β and the development of clinical trials of anakinra for treating children with KD. Continued effort is necessary to develop appropriate animal models of vasculitis that represent human diseases more faithfully and design alternative experimental systems to minimize animal suffering.

Considering infectious entities as potential causative agents of vasculitis is important. As described in this review, numerous microorganisms have been associated with human vasculitis. The clinical features vary according to the types of organisms, and even the same microorganism can cause different types of vasculitis. Tissue culture techniques, pathogen-specific histochemistry, or PCR with species-specific primers are typically employed to detect the causative pathogens [34]. Given that only a limited number of viruses have been detected using traditional techniques, unidentified viruses that can cause vasculitis may exist. Universal approaches involving the genetic sequencing of bacterial DNA, most commonly 16S ribosomal RNA gene sequencing for bacterial identification, have been widely adopted. Despite continued research, most studies have failed to detect the causative pathogens in human vasculitis, and the link between infection and vasculitis remains incompletely understood. For instance, the DNA sequencing of temporal artery biopsy samples from 17 patients with GCA and 5 controls did not reveal any distinctive microbiome signature in the patients [75]. However, the results of this study were influenced by the use of fixed and paraffin-embedded tissues, in which the DNA may be degraded. Moreover, only DNA microbes, such as bacteria, and DNA viruses can be detected using this method. Since vasculitis is occasionally associated with RNA viruses, including HCV, HIV, and even coronaviruses, as described in the present review, metagenomic next-generation sequencing that facilitates the unbiased characterization of all nonhuman nucleic acids could be beneficial for identifying the potential candidate pathogens in a sample. Further studies are necessary to confirm the presence of previously unidentified pathogens in human vasculitis, which is often considered an idiopathic disease. Further research is also necessary to verify the role of the pathogens in animal models to establish novel therapeutic strategies for pathogen-associated vasculitis.

## Article Information

# References

1. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1-11.

2. Fiorentino DF. Cutaneous vasculitis. J Am Acad Dermatol. 2003;48(3):311-40.

3. Feldstein LR, Rose EB, Horwitz SM, et al. Overcoming COVID-19 Investigators, CDC COVID-19 Response Team. Multisystem inflammatory syndrome in U.S. Children and adolescents. N Engl J Med. 2020;383(4):334-46.

4. Miyabe C, Miyabe Y, Bricio-Moreno L, et al. Dectin-2-induced CCL2 production in tissue-resident macrophages ignites cardiac arteritis. J Clin Invest. 2019;129(9):3610-24.

5. Thibault S, Drolet R, Germain MC, et al. Cutaneous and systemic necrotizing vasculitis in swine. Vet Pathol. 1998;35(2):108-16.

6. Henson JB, Crawford TB. The pathogenesis of virus-induced arterial disease--Aleutian disease and equine viral arteritis. Adv Cardiol. 1974;13:183-91.

7. Henson JB, Gorham JR. Persistent viral infections, immunologically mediated glomerulonephritis and arteritis, dysgammopathies. Aleutian disease of mink. Am J Pathol. 1973;71(2):345-8.

8. Chirnside ED. Equine arteritis virus: an overview. Br Vet J. 1992;148(3):181-97.

9. Wilczynski SP, Cook ML, Stevens JG. Newcastle disease as a model for paramyxovirus-induced neurologic syndromes. II. Detailed characterization of the encephalitis. Am J Pathol. 1977;89(3):649-66.

10. Kajima M, Pollard M. Arterial lesions in gnotobiotic mice congenitally infected with LCM virus. Nature. 1969;224(5215):188-90.

11. Parker JC, Igel HJ, Reynolds RK, et al. Lymphocytic choriomeningitis virus infection in fetal, newborn, and young adult Syrian hamsters (Mesocricetus auratus). Infect Immun. 1976;13(3):967-81.

12. Dangler CA, Baker SE, Kariuki NM, et al. Murine cytomegalovirus-associated arteritis. Vet Pathol. 1995;32(2):127-33.

13. Laitinen K, Laurila A, Pyhälä L, et al. Chlamydia pneumoniae infection induces inflammatory changes in the aortas of rabbits. Infect Immun. 1997;65(11):4832-5.

14. Fong IW, Chiu B, Viira E, et al. Rabbit model for Chlamydia pneumoniae infection. J Clin Microbiol. 1997;35(1):48-52.

15. Moody KD, Barthold SW, Terwilliger GA, et al. Experimental chronic Lyme borreliosis in Lewis rats. Am J Trop Med Hyg. 1990;42(2):165-74.

16. Barthold SW, Beck DS, Hansen GM, et al. Lyme borreliosis in selected strains and ages of laboratory mice. J Infect Dis. 1990;162(1):133-8.

17. Nakamura T, Yamamura J, Sato H, et al. Vasculitis induced by immunization with Bacillus Calmette-Guérin followed by atypical mycobacterium antigen: a new mouse model for Kawasaki disease. FEMS Immunol Med Microbiol. 2007;49(3):391-7.

18. Thomas L, Davidson M, McCluskey RT. Studies of PPLO infection. I. The production of cerebral polyarteritis by Mycoplasma gallisepticum in turkeys; the neurotoxic property of the Mycoplasma. J Exp Med. 1966;123(5):897-912.

19. Lehman TJ, Walker SM, Mahnovski V, et al. Coronary arteritis in mice following the systemic injection of group B Lactobacillus casei cell walls in aqueous suspension. Arthritis Rheum. 1985;28(6):652-9.

20. Noval Rivas MN, Arditi M. Kawasaki disease: pathophysiology and insights from mouse models. Nat Rev Rheumatol. 2020;16(7):391-405.

21. Rodó X, Curcoll R, Robinson M, et al. Tropospheric winds from northeastern China carry the etiologic agent of Kawasaki disease from its source to Japan. Proc Natl Acad Sci U S A. 2014;111(22):7952-7.

22. Miyabe C, Miyabe Y, Miura NN, et al. Am80, a retinoic acid receptor agonist, ameliorates murine vasculitis through the suppression of neutrophil migration and activation. Arthritis Rheum. 2013;65(2):503-12.

23. Miyabe C, Miyabe Y, Komiya T, et al. A sphingosine 1-phosphate receptor agonist ameliorates animal model of vasculitis. Inflamm Res. 2017;66(4):335-40.

24. Somer T, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. Clin Infect Dis. 1995;20(4):1010-36.

25. Lidar M, Lipschitz N, Langevitz P, et al. The infectious etiology of vasculitis. Autoimmunity. 2009;42(5):432-8.

26. Belizna CC, Hamidou MA, Levesque H, et al. Infection and vasculitis. Rheumatol (Oxf Engl). 2009;48(5):475-82.

27. Maya R, Gershwin ME, Shoenfeld Y. Hepatitis B virus (HBV) and autoimmune disease. Clin Rev Allergy Immunol. 2008;34(1):85-102.

28. Pagnoux C, Cohen P, Guillevin L. Vasculitides secondary to infections. Clin Exp Rheumatol. 2006;24(2 Suppl 41):S71-81.

29. Ferri C, Sebastiani M, Giuggioli D, et al. Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. Semin Arthritis Rheum. 2004;33(6):355-74.

30. Teng GG, Chatham WW. Vasculitis related to viral and other microbial agents. Best Pract Res Clin Rheumatol. 2015;29(2):226-43.

31. Zandman-Goddard G, Shoenfeld Y. HIV and autoimmunity.

Autoimmun Rev. 2002;1(6):329-37.

32. Cuellar ML. HIV infection-associated inflammatory musculoskeletal disorders. Rheum Dis Clin North Am. 1998;24(2):403-21.

33. Haq SA, Pagnoux C. Infection-associated vasculitides. Int J Rheum Dis. 2019;22(Suppl 1):109-15.

34. Clifford A, Hoffman GS. Evidence for a vascular microbiome and its role in vessel health and disease. Curr Opin Rheumatol. 2015;27(4):397-405.

35. Buggage RR. Ocular manifestations of human T-cell lymphotropic virus type 1 infection. Curr Opin Ophthalmol. 2003;14(6):420-5.

36. Haynes BF, Miller SE, Palker TJ, et al. Identification of human T cell leukemia virus in a Japanese patient with adult T cell leukemia and cutaneous lymphomatous vasculitis. Proc Natl Acad Sci U S A. 1983;80(7):2054-8.

37. Pipitone N, Salvarani C. The role of infectious agents in the pathogenesis of vasculitis. Best Pract Res Clin Rheumatol. 2008;22(5):897-911.

38. Kikuta H, Sakiyama Y, Matsumoto S, et al. Detection of Epstein-Barr virus DNA in cardiac and aortic tissues from chronic, active Epstein-Barr virus infection associated with Kawasaki disease-like coronary artery aneurysms. J Pediatr. 1993;123(1):90-2.

39. Lunardi C, Tinazzi E, Bason C, et al. Human parvovirus B19 infection and autoimmunity. Autoimmun Rev. 2008;8(2):116-20.

40. Lazzerini PE, Cusi MG, Selvi E, et al. Non-HCV-related cryoglobulinemic vasculitis and parvovirus-B19 infection. Joint Bone Spine. 2018;85(1):129-30.

41. Pether JV, Thurlow J, Palferman TG, et al. Acute hantavirus infection presenting as hypersensitivity vasculitis with arthropathy. J Infect. 1993;26(1):75-7.

42. Phinney PR, Fligiel S, Bryson YJ, et al. Necrotizing vasculitis in a case of disseminated neonatal herpes simplex infection. Arch Pathol Lab Med. 1982;106(2):64-7.

43. Larsson A, Forsgren M, Hård af Segerstad S, et al. Administration of interferon to an infant with congenital rubella syndrome involving persistent viremia and cutaneous vasculitis. Acta Paediatr Scand. 1976;65(1):105-10.

44. Esper F, Shapiro ED, Weibel C, et al. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis. 2005;191(4):499-502.

45. Shirato K, Imada Y, Kawase M, et al. Possible involvement of infection with human coronavirus 229E, but not NL63, in Kawasaki disease. J Med Virol. 2014;86(12):2146-53.

46. Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis. 2020;20(11):e276-88.

47. Henderson LA, Yeung RSM. MIS-C: early lessons from immune profiling. Nat Rev Rheumatol. 2021;17(2):1-2.

48. Gruber CN, Patel RS, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). Cell. 2020;183(4):982-95.e14.

49. Kiselev D, Matsvay A, Abramov I, et al. Current trends in diagnostics of viral infections of unknown etiology. Viruses. 2020;12(2).

50. Cohen Tervaert JW. Trimethoprim-sulfamethoxazole and antineutrophil cytoplasmic antibodies-associated vasculitis. Curr Opin Rheumatol. 2018;30(4):388-94.

51. Popa ER, Tervaert JW. The relation between Staphylococcus aureus and Wegener's granulomatosis: current knowledge and future directions. Intern Med. 2003;42(9):771-80.

52. Kinumaki A, Sekizuka T, Hamada H, et al. Characterization of the gut microbiota of Kawasaki disease patients by metagenomic analysis. Front Microbiol. 2015;6:824.

53. Hashkes PJ. 50 years Ago in The Journal of Pediatrics: anaphylactoid Purpura: streptococcal antibody Titers and β(1c)-globulin Levels. J Pediatr. 2019;211:111.

54. Chaudhry AR, Chaudhry MR, Papadimitriou JC, et al. Bartonella henselae infection-associated vasculitis and crescentic glomerulonephritis leading to renal allograft loss. Transpl Infect Dis. 2015;17(3):411-7.

55. Soto ME, Del Carmen Ávila-Casado M, Huesca-Gómez C, et al. Detection of IS6110 and HupB gene sequences of Mycobacterium tuberculosis and bovis in the aortic tissue of patients with Takayasu's arteritis. BMC Infect Dis. 2012;12:194.

56. Pandhi D, Kaur I, Singal A, et al. Atypical presentation of immunoglobulin A vasculitis in disseminated tuberculosis. Int J Dermatol. 2019;58(1):e1-3.

57. Carod Artal FJ. Clinical management of infectious cerebral vasculitides. Expert Rev Neurother. 2016;16(2):205-21.

58. Kim HM, Park YB, Maeng HY, et al. Cutaneous leukocytoclastic vasculitis with cervical tuberculosis lymphadenitis: a case report and literature review. Rheumatol Int. 2006;26(12):1154-7.

59. Shah SM, Howard RS, Sarkies NJ, et al. Tuberculosis presenting as retinal vasculitis. J R Soc Med. 1988;81(4):232-3.

60. Pulimamidi S, Caputo FJ, Fraimow HS, et al. Salmonella aortitis treated with endovascular aortic repair. Ann Vasc Surg. 2014;28(5):1314.e5-10.

61. Sailors DM, Eidt JF, Gagne PJ, et al. Primary Clostridium septicum aortitis: a rare cause of necrotizing suprarenal aortic infection. A case report and review of the literature. J Vasc Surg. 1996;23(4):714-8.

62. Guillevin L. Infections in vasculitis. Best Pract Res Clin Rheumatol. 2013;27(1):19-31.

63. Blair JE. Coccidioidal meningitis: update on epidemiology, clinical features, diagnosis, and management. Curr Infect Dis Rep. 2009;11(4):289-95.

64. Ioannou P, Papakitsou I, Kofteridis DP. Fungal endocarditis in transplant recipients: A systematic review. Mycoses. 2020;63(9):952-63.

65. Jud P, Valentin T, Regauer S, et al. Invasive Candida krusei infection and Candida vasculitis of a leg ulcer in an immunocompetent patient: A case report. Int J Infect Dis.

2017;55:196-8.

66. Collins GJ, Jr., Rich NM, Hobson RW, et al. Multiple mycotic aneurysms due to Candida endocarditis. Ann Surg. 1977;186(2):136-9.

67. Edelson RN, McNatt EN, Porro RS. Candida meningitis; with cerebral arteritis. N Y State J Med. 1975;75(6):900-4.

68. Dourmishev LA, Dourmishev AL. Syphilis: uncommon presentations in adults. Clin Dermatol. 2005;23(6):555-64.

69. Kim DH, Choi SR, Lee KR, et al. Syphilis showing leukocytoclastic vasculitis. J Cutan Pathol. 2010;37(5):607-8.

70. Rajapakse S, Weeratunga P, Sivayoganathan S, et al. Clinical manifestations of scrub typhus. Trans R Soc Trop Med Hyg. 2017;111(2):43-54.

71. Oksi J, Kalimo H, Marttila RJ, et al. Inflammatory brain changes in Lyme borreliosis. A report on three patients and review of literature. Brain. 1996;119(6):2143-54.

72. Leys AM, Schönherr U, Lang GE, et al. Retinal vasculitis in Lyme borreliosis. Bull Soc Belge Ophtalmol. 1995;259:205-14.

73. Pizzarello LD, MacDonald AB, Semlear R, et al. Temporal arteritis associated with Borrelia infection. A case report. J Clin Neuroophthalmol. 1989;9(1):3-6.

74. Christen U. Pathogen infection and autoimmune disease. Clin Exp Immunol. 2019;195(1):10-4.

75. Bhatt AS, Manzo VE, Pedamallu CS, et al. In search of a candidate pathogen for giant cell arteritis: sequencing-based characterization of the giant cell arteritis microbiome. Arthritis Rheumatol. 2014;66(7):1939-44.