Known infectious causes of vasculitis in man

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An array of pathogens is known to cause vasculitis in man.[1,2] For several of these agents, vasculitis is the major manifestation of disease. The majority, however, typically present as infectious processes in which vasculitis is an occasional manifestation of disease. For many, vasculitis may be a component of disease pathogenesis but is not a prominent feature of the clinical presentation. The various agents—viruses, bacteria, and fungi—share a common target, blood vessels. The involvement of vessels may be direct, with vascular structures serving as targets. Many infectious pathogens have tissue tropism that includes endothelium. Other agents may bind to the vessel wall because the vascular endothelium expresses specific receptors for the pathogen or another moiety with which the pathogen travels. Even when the agent does not enter the endothelial cell, the immune response to the agent may be focused at the vessel wall because the pathogen is adherent to the endothelial cell surface, thereby promoting innocent by-stander injury to the vessel. Processes that target the endothelium directly are usually acute in nature. Innocent bystander injury is often chronic and may be insidious in onset.

Demonstration of infectious agents as the cause of some cases of vasculitis fuels interest in searching for infectious etiologies of idiopathic vasculitis. The advent of highly sensitive molecular techniques has encouraged searches for various known pathogens in idiopathic vasculitis. Recognition that infectious agents are dynamic populations of organisms prompts us to search for emerging pathogens as previously unknown causes of vasculitis. Such pathogens "emerge" as new species or strains develop from older species in their traditional host population. Others may emerge due to spread into a new host population. The new, previously non-susceptible population may become infected because the pathogen adapts to the new host species. Alternatively, the agent may spread to a new susceptible host population as a consequence of changes in the physical environment or human or vector behavior that promotes geographical spread. In mirror fashion, changes in the behavior of pathogens, vectors, and hosts, and our ability to intervene in disease processes, have rendered some causes of vasculitis far less common.

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VIRAL CAUSES OF VASCULITIS

Our knowledge of viral pathogenesis has exploded in the last quarter of the twentieth century, accelerated in large part by epidemics of "emerging" viral diseases. Hepatitis C virus, discovered in 1989, has worldwide prevalence.[3] The 10- to 20-year latent period before hepatic or rheumatic manifestations of disease explains the increasing number of cases of hepatitis C virus–mediated vasculitis currently being seen in the United States following the epidemic of new infections in the 1980s.[4] Prior to the discovery and characterization of hepatitis C virus in the late 1980s, the triad of arthritis, palpable purpura, and type II cryoglobulinemia was given the sobriquet "essential mixed cryoglobulinemia" and considered an idiopathic vasculitis. Availability of diagnostic testing for hepatitis C virus demonstrated that almost all of these cases were associated with hepatitis C virus infection. Immune response to the virus elicits a response to the Fc portion of immunoglobulin with the majority of elicited antibody having the Wa idiotype.[5,6] Immune complexes of anti–Fc Wa idiotypic antibody and pre-existing antibody, and virus have the peculiar physical property of precipitating out of solution in the cold ("cryoglobulins"). Presumably, Wa idiotype recognizes a cross-reactive epitope found on hepatitis C virus and immunoglobulin. Extremities and skin are sufficiently cold so as to explain a predilection for small-vessel leukocytoclastic vasculitis of the skin; gravity enhances vascular injury in dependent distal vessels, giving rise to palpable purpura predominantly in the lower extremities. More severe cases may manifest visceral organ involvement including membranoproliferative glomerulonephritis and bowel involvement. Small- and medium-sized arteries may be involved as well, especially in the kidneys.

Hepatitis B virus (HBV) infection provides the classic example of virally mediated immune complex disease. A lymphocytic venulitis or neutrophilic vasculitis of small vessels with leukocytoclastic or fibrinoid changes presents typically as an "urticaria-arthritis syndrome."[7] Immune complexes of hepatitis B virus surface antigen (HBsAg) and antibodies to hepatitis B virus surface antigen (HBsAb) circulate in the blood and are found deposited in vessels in association with complement.[8,9] The long latency period of HBV allows time for an immune response to occur. Viral replication increases HBsAg load, and is tem-

porally associated with jaundice.[10] The immune complexes eventually no longer form in antigen excess, and the serum sickness-like illness resolves. HBV has also been associated with large-vessel polyarteritis nodosa-like illness.[11] Onset is early in the course of chronic HBV hepatitis. Immune complexes containing HBsAg, HBsAb, and complement are found in the vessel wall.[12] The determinants of small vessel versus larger vessel disease in the two syndromes of HBV infection are unknown.

Human immunodeficiency virus (HIV) patients may present with a variety of vasculitides. However, it is difficult to specifically attribute the various vasculitides seen to HIV because of frequent co-infections with other agents that may cause vasculitis in the absence of HIV infection. Human T lymphotropic virus 1 infection may cause retinal, cutaneous, or central nervous system vasculitis.[13-16]

The herpesviruses (cytomegalovirus, varicella-zoster, herpes simplex viruses 1 and 2, and herpes hominis) may be associated with retinal vasculitis in immunocompromised patients.[17-23] Varicella-zoster may also cause a diffuse central nervous system small arterial granulomatous vasculitis, or a small- and/or large-artery vasculopathy.[24-27] Herpes simplex viruses 1 and 2 have been associated with cutaneous vasculitis and necrotizing arteritis of small and medium vessels.[28-30] Epstein-Barr virus has been suggested as a cause of both small- and large-vessel disease in a number of cases and short series.[31-36] However, the ability to demonstrate causality in many instances is made all the more difficult by the latency of herpesvirus infection.

Parvovirus B19 has been suggested as the causative agent of Wegener's granulomatosis and polyarteritis nodosa in a number of cases and short series.[37-42] However, the issue of latency and the failure to eliminate B19 from pooled blood products provides a cautionary note when considering causality.[43-46] Rare cases of vasculitis have similarly been reported following rubella virus, adenovirus, echovirus, coxsackievirus, parainfluenza virus, herpes simplex viruses, and hepatitis A virus infections.[1,47-57]

■ BACTERIAL CAUSES OF VASCULITIS

Bacterial seeding of vessels may lead to necrosis through direct bacterial action. Vessels may be seeded intraluminally at sites of endothelial injury or flow turbulence. Seeding of vasa vasora may cause destruction of vessels from the outside in. An injury of a large vessel by this mechanism is classically termed a "mycotic aneurysm." Contiguous spread from an infected site to a vessel may occur. Vessels may also be seeded from within the lumen, as in subacute bacterial endocarditis in which septic emboli embed within the wall of smaller vessels, causing a "mycotic" process via a luminal route. Immune response to bacteria or to bacterial components may also lead to vasculitis, usually by immune-complex–mediated mechanisms.[2]

In subacute bacterial endocarditis, direct spread via septic emboli and immune complex injury may occur. Patients may present with evidence of elevated acute-phase reactants, fever, malaise, myalgia, arthralgia, Osler's nodes, Janeway lesions, and septic infarcts.[58,59] Staphylococcus and streptococcus infections are common causes. Gram-negative organisms, other gram-positive cocci, fungi, and parasites may be causative as well, and their occurrence depends on the clinical setting.[60-66] Mycotic aneurysms resulting from septic emboli are common with staphylococcus, streptococcus, and *Salmonella* species.[67-69] Patients with subacute infections may develop cryoglobulins.[70-72] Bacteremia may present as leukocytoclastic vasculitis.[73,74] Small-vessel vasculitis may be associated with post-streptococcal infection, distinct from endocarditis.[75,76] The *Rickettsiae* are a group of obligate intracellular bacteria with tropism for vascular endothelium.[77] Infection results in widespread microvascular leak, local thrombosis, and ultimately multisystem failure if untreated.[78,79]

In the lung, necrosis of vessels may occur from septic emboli or from contiguous spread in primary pneumonias. In the latter setting, *Pseudomonas aeruginosa* and *Legionella pneumophila* often cause direct necrosis via contiguous spread.[80] The presentation, however, is that of pneumonia. Mycobacterial or fungal pulmonary infections may mimic Wegener's granulomatosis or Churg-Strauss vasculitis in eliciting a granulomatous reaction in vessels.[81] Spread of *Mycobacterium tuberculosis* to the aorta may be seen as a cause of tuberculous aortitis, coronary arteritis, and mycotic aneurysm.[82-84] *Aspergillus aeruginosa*, *Aspergillus fumigatus*, and *Mucor* may be characterized by direct vessel invasion and necrosis.[68,85,86]

Coccidioides immitis meningitis may be associated with vasculitis that can be confused with central nervous system angiitis.[87,88] *Coccidioides immitis* may also present as an immune-complex–mediated disease with erythema nodosum, periarthritis predominantly of the ankles, and bihilar lymphadenopathy.[89,90] This presentation is often confused with Löfgren's syndrome of sarcoidosis. While sarcoidosis as a cause of Löfgren's syndrome is more prevalent in eastern United States populations, *Coccidioides immitis* is a more likely cause of a Löfgren's-like presentation in the western United States.

Neisseria species may be associated with small-vessel vasculitis. In *Neisseria gonorrhea* infection, cutaneous papules vesiculate, then becomes necrotic.[91] In *N meningitides* infections, vasculitis may manifest in the skin and gastrointestinal tract with the endothelium showing necrosis and thrombosis.[92-94] In immunocompromised hosts, *Pseudomonas aeruginosa* and other gram-negative organisms can present as a large 1- to 5-cm macular erythema that develops central necrosis and peripheral edema and induration—a condition termed "ecthyma gangrenosum." Vessel thrombosis results from direct bacterial invasion of the vessels. Similar lesions may be seen in immunocompromised patients with disseminated *Pseudomonas*, *Nocardia*, *Aspergillus*, *Mucor*, *Curvularia*, *Pseudallescheria*, *Fusarium*, *Morganella*, *Metarrhizium*, *Xanthomonas*, *Klebsiella*, *E coli*, and *Aeromonas* infections.[95-107]

Before AIDS, syphilis was the infectious agent known as the "great imposter," presenting as large- or medium-size vessel disease (aortitis or coronary arteries) or as the small-vessel rash of secondary lues. Aortic aneurysms

were insidious in clinical presentation. *Treponema pallidum* spirochetes were rarely detected in fibrosed and scarred vessels.[108-110] At least briefly, *Borrelia burgdorferi*, the causative agent of Lyme disease, was known as an "imposter." Vasculitic changes may be seen in the central nervous system, retina, and temporal arteries.[111-124]

Parasites are a rare cause of vasculitis. The local response to a parasite may include vessel changes typical of vasculitis, but these are localized to the offending pathogen. In a few instances, however, more distant effects have been reported. *Toxocara canis* presented in an adolescent as palpable purpura with additional features suggesting Henoch-Schönlein purpura.[125] *Cysticercus* has caused vasculitis and arachnoiditis as it infects the central nervous system.[126] *Angiostrongylus* nematodes apparently caused a Wegener's granulomatosis-like pulmonary angiitis.[127] *Loa loa*, a filarial parasite, presented with cutaneous leukocytoclastic vasculitis.[128]

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