



# Infections in primary vasculitides

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**A**therosclerosis and vasculitis are both inflammatory vascular disorders. In lesions of both disorders T lymphocytes are found that are clonally expanded, suggesting an antigen-driven immune response.<sup>1,2</sup> The antigens involved are, however, not well characterized in most cases. Auto-antigens and/or microbial antigens are likely candidates. In atherosclerosis, several infectious agents have been proposed such as cytomegalovirus, *Chlamydia pneumoniae*, and *Helicobacter pylori*.<sup>3</sup> Also, vasculitis is linked to a wide variety of microbes.<sup>4,5</sup> Classic examples are syphilitic aortitis, vasculitis of the skin related to subacute bacterial endocarditis, and hepatitis-B-associated polyarteritis nodosa (PAN). More recently, evidence was found that also in the so-called primary or idiopathic forms of vasculitis, microbes could play a role in the pathophysiology of these diseases. The mechanisms that could be operative in these latter will be discussed in this review.

## ■ LARGE-VESSEL VASCULITIDES

Several bacteria and fungi cause large-vessel vasculitis. So-called mycotic aneurysms are nowadays more frequently caused by *Salmonella*, *Campylobacter*, *Yersinia*, *Pseudomonas*, and other gram-negative bacteriae and anaerobes than the classic examples such as syphilis, mycobacteria, and/or aspergillus.<sup>4</sup> Primary large-vessel vasculitides, ie, giant-cell arteritis and Takayasu's arteritis, have no clearly established association with an infection, although previous exposure to mycobacterial, streptococcal, or spirochetal infection has often been mentioned in Takayasu's arteritis.

## ■ VASCULITIS INVOLVING MEDIUM- AND SMALL-SIZED ARTERIES

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is a form of systemic vasculitis of unknown cause that primarily affects infants and young children. Clinical features include acute fever; cervical lymphadenopathy; conjunctival injection; redness of the lips, tongue, or oral mucosa; erythema of the palms and soles; edema of the hands and feet; a polymorphous cuta-

neous rash; desquamation of the skin; and cardiac abnormalities in about 20–30% of the patients. Arteritis of the coronary, iliac, or other systemic arteries can be found on histologic examination. The syndrome can occur sporadically, but sometimes clear outbreaks are observed. Several infectious agents have been suspected to be responsible for the syndrome such as streptococci, staphylococci, Epstein-Barr virus (EBV), retrovirus, or parvovirus B19.<sup>4</sup> In a few cases a clear pathophysiological role for toxic shock syndrome toxin-1 (TSST-1)-positive *Staphylococcus aureus* has been documented.<sup>6</sup>

In PAN, immune-complex and complement deposits are often found in involved tissues.<sup>4</sup> An infectious agent has to be searched for and is often found. In children,  $\beta$ -hemolytic group A streptococci are especially associated with PAN. In adults, hepatitis B virus (HBV) infection has a firm link with PAN. During recent years, however, a decline in HBV-related PAN has been documented in France, and at present less than 10% of PAN cases are HBV positive.<sup>7</sup> PAN-like disease has been found increasingly often, however, in patients that are infected with HIV.<sup>5</sup> Whether PAN in these cases is a result of a direct effect of HIV infection of blood vessels, a result of the immune activation that accompanies HIV infection, or a result of accompanying drug hypersensitivity or complicating infections with viruses such as CMV, HBV, or hepatitis C virus, is at present unknown.<sup>5</sup> Finally, many other incidental microbial associations with PAN-like vasculitis has been described (reviewed in 4).

## ■ VASCULITIS INVOLVING SMALL-SIZED VESSELS

In a few children with Wegener's granulomatosis (WG), a disease characterized by chronic inflammation of the respiratory tract, glomerulonephritis, and vasculitis, chronic parvovirus B19 has been suspected.<sup>5</sup> In adults, however, this virus is not found. A more important infectious association in WG is chronic nasal carriage of *S aureus*.<sup>8</sup> Previously, we found that 60–70% of our patients were chronic nasal carriers of *S aureus* and that those patients that were chronically carrying *S aureus* relapsed nearly eight times more frequently than noncarriers.<sup>9</sup> Recently, we found that 40–50% of the *S aureus* strains that are found in these nasal cultures are positive for staphylococcal superantigens.<sup>6,8,10</sup> Superantigens that were most frequently found were TSST-1, staphylococcal enterotoxin A and C, and exfoliative toxin A. Importantly, in a long-term observational study, we found that TSST-1-positive *S aureus* strains but not strains that

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were positive for other superantigens increased the risk for a relapse of WG.<sup>10</sup> Another observation that links WG with bacterial infection and/or colonization is the finding that patients with WG in which the disease is restricted to the respiratory tract can be successfully treated with co-trimoxazole as monotherapy.<sup>11</sup> Furthermore, we previously demonstrated in a placebo-controlled trial that co-trimoxazole maintenance therapy in patients with WG not only reduced the infection rate but also reduced the risk to develop a relapse by more than 60%.<sup>12</sup> It has been postulated that co-trimoxazole may exert this effect by eradication of chronic nasal *S aureus* carriage. In a recent study, however, we were unable to demonstrate such an effect since nasal *S aureus* carriage was terminated in only 5 of 21 WG patients during co-trimoxazole maintenance therapy. This finding suggests that co-trimoxazole exerts its beneficial effect in WG through a different mechanism, possibly an anti-inflammatory action. Importantly, it has been demonstrated in *in vitro* studies that co-trimoxazole inhibits myeloperoxidase-mediated halogenation of proteins.

In the other two forms of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides, ie, microscopic polyangiitis and the Churg-Strauss syndrome (CSS), the role of chronic nasal *S aureus* carriage is less clear. Cases have been described in which CSS was linked to infection with *Ascaris*, *Aspergillus fumigatus*, and/or HIV.<sup>4</sup> In addition, in several CSS cases a link with immunostimulation due to vaccination and/or desensitization is suspected (but never proven).

In Henoch-Schönlein purpura and isolated leukocytoclastic vasculitis of the skin, a precipitating microbial agent is often found. Bacteria, viruses, and sometimes parasites, such as *Ascaris*, have been associated with these forms of small-vessel vasculitis.<sup>4</sup> Microorganisms that are most frequently involved are streptococci, staphylococci, neisseriae, cytomegalovirus, parvovirus B19, HIV, HBV, and hepatitis C virus. Vasculitic lesions in these patients are assumed to be the result of immune-complex deposition initiated by microbial antigens. In some cases, however, other mechanisms may be operative such as in rickettsiae infections, in which infections primarily infect and damage endothelial cells resulting in vasculitis.

During the past decade, it became clear that there is a firm link between hepatitis C virus infection (HCV) and mixed essential cryoglobulinemia (MEC).<sup>13</sup> Patients with MEC due to HCV often suffer from palpable purpura and arthralgias; furthermore, many patients have hepatic, renal, and neurologic involvement. In the majority of MEC patients, hypocomplementemia and circulating rheumatoid factors can be detected. Whereas in Mediterranean countries more than 80% of the patients are positive for HCV RNA as detected by polymerase chain reaction, it is assumed that MEC in Northern European countries is less often associated with HCV. Cryoprecipitates in patients with HCV-associated MEC may contain both HCV and specific antibodies to HCV. Furthermore, HCV has been demonstrated in vasculitic skin lesions.<sup>13</sup>

## ■ MECHANISMS BY WHICH INFECTIOUS AGENTS TRIGGER VASCULITIS

Different mechanisms may be operative in the induction of vasculitis by infectious agents.<sup>6</sup> Three mechanisms are most likely to be involved: a) direct microbial invasion of endothelial cells; b) participation in immune-complex mediated damage of vessel walls; and c) stimulation of (auto-reactive) B and/or T lymphocytes.

### A. Direct microbial invasion

Rickettsiae are responsible for Rocky Mountain spotted fever, a disease which is characterized by a vasculitic rash. Rickettsiae primarily infect the endothelium of the microvasculature and later on also endothelial cells of small arteries and veins. Another example of microbial invasion of endothelial cells is *S aureus*. It has been demonstrated that *S aureus* binds more readily to endothelial cells than most other bacteria. Following binding, bacteria are internalized and can persist in phagosome-like vacuoles as small colony variants. The interaction between *S aureus* and endothelial cells may result in activation of the endothelial cells resulting in enhanced expression of adhesion molecules such as P-selectin and ICAM-1 and in the production of cytokines and chemoattractants such as IL-8 and MCP-1. Furthermore, endothelial cells may be damaged following internalization of alpha-toxin producing strains.

### B. Immune-complex-mediated damage of vessel walls

In biopsies of patients with vasculitis, deposits of immunoglobulins and complement components are often found. The nature of the antigen is, however, in most cases unknown. In skin biopsies with vasculitis due to MEC, HCV has been identified.<sup>13</sup> Since electrical charge is an important factor for antigen deposition, we studied the possibility that cationic staphylococcal antigens may be involved in immune-complex formation in WG. We found that one of these proteins, staphylococcal acid phosphatase (SACP), had *in vitro* high affinity for endothelial cells and that renal perfusion of SACP in SACP-immunized rats resulted in a severe crescentic glomerulonephritis. Furthermore, antibodies to SACP were frequently detected in patients with WG, and SACP was present in 3 of 19 renal biopsies from patients with WG.<sup>14</sup> From these studies, we hypothesized that in WG immune complexes play a role in the initiation of the disease and that staphylococcal antigens are likely candidate antigens.

### C. Stimulation of (autoreactive) B and/or T lymphocytes

Infections may stimulate autoimmune responses by different mechanisms.<sup>6</sup> These include shared epitopes between pathogens and host, upregulation of heat shock proteins, and stimulation of lymphocytes by factors such as peptidoglycan, protein A, CpG motifs in bacterial DNA, and superantigens. Superantigens are extremely potent activators of lymphocytes. Stimulation of T cells is dependent on the presence of MHC class II molecules on antigen-presenting cells. In contrast to classical T-cell

antigens, processing of the superantigens is not needed. Superantigens bind to MHC class II molecules on antigen-presenting cells and to conserved regions of T-cell receptor V-beta chains. Virtually all T cells expressing a superantigen-binding V-beta chain proliferate. After proliferation, activated T cells undergo apoptosis. Furthermore, repetitive stimulation may induce anergy, a process that is possibly dependent on stimulation of CD4+ regulatory T cells. Superantigens may induce autoimmunity by stimulation of autoreactive cytotoxic T cells and/or by T-cell-dependent activation of antigen-specific B cells. In Kawasaki disease vasculitic disease activity, TSST-1 producing *S aureus*, and the presence of corresponding V-beta

2+ T cells have been simultaneously documented.<sup>6</sup> In patients with WG, a condition in which T-cell expansions and staphylococcal superantigens are frequently found, we failed to show superantigen-related T-cell expansions.

## ■ CONCLUSION

Infectious agents have been clearly demonstrated in various vasculitides. Direct evidence of a pathophysiological role of specific microbial agents is, however, scarce. Recently developed molecular approaches such as DNA microarrays may be helpful for studying this issue in the near future.

## ■ REFERENCES

1. Goronzy JJ. T cells in vascular disease. In: Hoffman GS, Weyand CM. Inflammatory diseases of blood vessels. Marcel Dekker, New York, 2002:57-68.
2. Hansson GK. Cell-mediated immunity in atherosclerosis. *Curr Opin Lipidol* 1997; 8:301-311.
3. Juvonen T, Juvonen J, Savolainen MJ. Is vasculitis a significant component of atherosclerosis? *Curr Opin Rheumatol* 1999; 11:3-10.
4. Somer T, Finegold SM. Vasculitides associated with infections, immunization, and antimicrobial drugs. *Clin Infect Dis* 1995; 20:1010-1036.
5. Mandell BF, Calabrese LH. Infections and systemic vasculitis. *Curr Opin Rheumatol* 1998; 10:51-57.
6. Cohen Tervaert JW, Popa ER, Bos NA. The role of superantigens in vasculitis. *Curr Opin Rheumatol* 1999; 11:24-33.
7. Guillevin L, Lhote F, Cohen P, et al. Polyarteritis nodosa related to hepatitis B virus. A prospective study with long-term observation of 41 patients. *Medicine (Baltimore)* 1995; 74:238-253.
8. Cohen Tervaert JW, Popa ER, Brons RH. Staphylococcal aureus, superantigens and vasculitis. *Clin Exp Immunol* 2000; 120(suppl 1):6-7.
9. Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med* 1994; 120:12-17.
10. Popa ER, Stegeman CA, Van der Meer B, et al. Staphylococcus toxic-shock-syndrome toxin-1 (TSST-1): a risk factor for disease exacerbation in Wegener's granulomatosis. Abstract 4-093.
11. Cohen Tervaert JW, Stegeman CA, Kallenberg CG. Novel therapies for anti-neutrophil cytoplasmic antibody-associated vasculitis. *Curr Opin Nephrol Hypertens* 2001; 10:211-217.
12. Stegeman CA, Cohen Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. *N Engl J Med* 1996; 335:16-20.
13. Agnello V, Romain PL. Mixed cryoglobulinemia secondary to hepatitis C virus infection. *Rheum Dis Clin North Am* 1996; 22:1-21.
14. Brons RH, Kallenberg CG, Cohen Tervaert JW. Are antineutrophil cytoplasmic antibody-associated vasculitides pauci-immune? *Rheum Dis Clin North Am* 2001; 27:833-48.