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Vasculitis and infections: Contribution to the issue of autoimmunity reviews devoted to "autoimmunity and infection"

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ABSTRACT

Infections are associated with secondary forms of vasculitis. However, there is increasing evidence that microbial agents play a role also in primary systemic vasculitides. For a long time it has been noted that Hepatitis B virus (HBV) is involved in polyarteritis nodosa (PAN) although the incidence of HBV-associated PAN seems to decline. Cryoglobulinemic vasculitis has been shown to be strongly associated with Hepatitis C Virus (HCV) infection, but this is most striking in Southern Europe and less in Northern Europe. Different microbial agents have been suggested to influence disease expression in other primary vasculitides but no specific association has been established. In Wegener's Granulomatosis (WG) chronic carriage of *Staphylococcus aureus* (*S. aureus*) is associated with a strongly increased risk for relapsing disease. Various pathogenic pathways for this association have been suggested by clinical and experimental observations. Recent studies even suggest that *S. aureus* derived peptides, amongst others, may induce proteinase 3-ANCA via idiotypic–anti-idiotypic interactions. Treatment with co-trimoxazole in WG localized to the upper airways may result in (temporary) remission of the disease.

Contents

1. Introduction

Vasculitis is defined as an inflammatory process of blood vessels. It can be secondary to other conditions or constitute a primary, in most cases idiopathic disorder. Underlying conditions in the secondary vasculitides are infectious diseases [1], connective tissue diseases, and hypersensitivity disorders. Immune complexes, supposedly composed of microbial antigens in case of underlying infectious diseases, autoantigens in the connective tissue diseases, and non-microbial exogenous antigens in the hypersensitivity disorders, are involved, in many cases, in the pathophysiology of the secondary vasculitides (Table 1). Besides, infectious agents may directly invade the blood vessel wall leading to vasculitis [1]. The primary vasculitides, classified according to the size of the vessels involved, the histopathology of the lesions, and certain clinical

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Table 1
Secondary vasculitides: antigens presumably involved

- •Exogenous antigens
  - Microbial antigens
    - Bacterial
      - *Streptococci*
      - *Staphylococci*
      - *Mycobacterium leprae*
      - *Treponema pallidum*
      - Others
    - Viral
      - Hepatitis B/C virus
      - Human immunodeficiency virus
      - Cytomegalovirus
      - Epstein–Barr virus
      - Others
    - Protozoal
      - Plasmodia
  - Non-microbial antigens
    - Heterologous proteins such as chimeric monoclonal antibodies
    - Allergens
    - Drugs
    - Tumor antigens (?)
- •Autologous antigens
    - Nuclear antigens (antinuclear antibodies)
    - Immunoglobulin G (rheumatoid factor, cryoglobulins)
    - Others

symptoms (Table 2), are, as mentioned, considered idiopathic conditions in most of the cases. There is, however, increasing evidence that microbial agents/infections play a role in the pathogenesis of primary vasculitides as well. In this review, the role of infectious agents in the primary vasculitides will be discussed. Special attention will be given to Wegener's Granulomatosis.

2. Large and medium-sized vessel vasculitides

Initial studies have suggested that parvovirus B19 and Herpes viruses, including Herpes Simplex Virus, Varizella-Zoster-Virus, and Human Herpes Virus 6, are involved in the pathogenesis of giant cell arteritis [3,4]. The presence of these viruses in lesional tissues from patients with this disease has been suggested based on positive PCR results. More recent studies, with larger numbers of patients and inclusion of adequate control tissue, could, however, not confirm these findings [5,6]. Furthermore, based on seasonal and geographical variation in presentation, infectious agents have been suggested in giant cell arteritis but proof for their involvement is lacking.

In Takayasu arteritis, infectious agents have not been demonstrated to be involved in disease pathogenesis. However, cellular immune responses against mycobacterial proteins, in particular heat shock proteins, have been observed in patients with Takayasu arteritis [7]. The relevance of this finding for the pathogenesis of the disease is highly questionable as such responses are present in healthy controls as well. One should, however, be aware that aortitis may result from infection, particularly syphilis.

With respect to the medium-sized vasculitides, polyarteritis nodosa (PAN) associated with Hepatitis B virus (HBV) infection has been noted for a long time. Depending on the geographical area, in particular the prevalence of HBV infection in that area, different percentages are given, but around 30% of patients with PAN are carriers of HBV [8]. Testing for HBV in patients with PAN is important as HBV infection determines clinical presentation, treatment and outcome. In patients with HBV-PAN, glomerulonephritis, ANCA-positivity, and relapsing disease are almost never found [8]. Treatment now consists of corticosteroids together with antiviral agents and plasma exchange. Treatment should be aimed at attaining seroconversion and stopping viral replication which, generally, results in complete remission of the disease without occurrence of relapses and in prevention of long-term hepatic complications [8]. PAN-like syndromes have also been reported in patients with human immunodeficiency virus (HIV) infection. Different vasculitic syndromes can be encountered in these patients, including PAN, Kawasaki-like syndromes, primary angiitis of the central nervous system, and small vessel vasculitis [9,10]. In many cases symptoms are not very specific and may suggest manifestations of HIV-disease itself, resulting in delay in diagnosis and treatment of the associated vasculitis.

Kawasaki disease is an intriguing inflammatory vasculitis of early childhood in which the coronary arteries are frequently affected. It has been suggested that the disease results from an abnormal immunological response to, possibly, various microbial agents in genetically susceptible infants. Viruses have been suggested to be involved, such as the New Haven Corona Virus, HIV, adenovirus, etc. [11]. Also superantigens derived from *Staphylococcus aureus* have been implicated [12]. Superantigens are proteins that bind to MHC class II molecules on antigen presenting cells and interact simultaneously with specific Vβ segments of the T-cell receptor (TCR). As such, they are able to stimulate, in an antigen-independent way, all T-cells that utilize a particular group of TCR Vβ segments. In Kawasaki disease, *S. aureus* strains have been isolated expressing various superantigens, in particular the toxic-shock-syndrome toxin-1 (TSST-1) superantigen, and analysis of the Vβ repertoire on the TCR of circulating T-cells showed T-cell expansion compatible with superantigen driven T-cell proliferation [12]. However, the exact role of *S. aureus* in Kawasaki disease is far from clarified.

3. Small vessel vasculitides

In the small vessel vasculitides infectious agents have been suggested to be involved in disease pathogenesis in various disorders.

Hepatitis C virus (HCV) infection, having a global prevalence of around 2%, is associated with mixed cryoglobulinemia in around 50% of infected patients, and with cryoglobulinemic vasculitis in 5–10% of patients. There are striking differences in

Table 2
Classification of primary vasculitides according to the Chapel Hill Consensus Conference [2]

- I. Large vessel vasculitis
  1. Giant cell (temporal) arteritis
  2. Takayasu arteritis
- II. Medium-sized vessel vasculitis
  1. Polyarteritis nodosa
  2. Kawasaki disease
- III. Small vessel vasculitis
  1. Wegener's Granulomatosis *
  2. Churg–Strauss syndrome *
  3. Microscopic polyangiitis *
  4. Henoch Schönlein purpura
  5. Essential cryoglobulinemia vasculitis
  6. Cutaneous leukocytoclastic angiitis

* ANCA-associated.

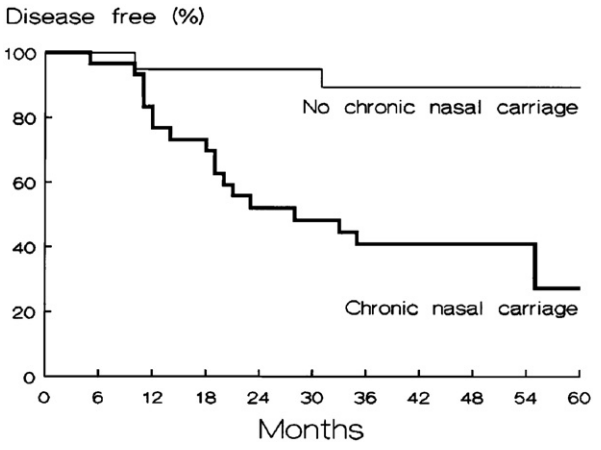

Fig. 1. Disease-free interval of 57 patients with Wegener's granulomatosis grouped according to *Staphylococcus aureus* carrier status. The time of the disease-free interval was counted from the beginning of the most recent period of disease activity (either initial diagnosis or relapse; $p < 0.001$). From Ref. [18], with permission.

these percentages between patients from Northern Europe and those from Southern Europe, in particular Italy. Whereas only a minority of patients with mixed cryoglobulinemic vasculitis in Northern Europe is positive for HCV, the majority of patients with this disorder from Italy tests positive. The reason for this difference is not known. The clinical spectrum of this form of vasculitis is variable ranging from purpura to severe proliferative glomerulonephritis [13]. How HCV induces B-cell activation and proliferation, resulting in the production of monoclonal rheumatoid factor, an essential component of mixed cryoglobulins, is presently not clear. However, the detection of HCV in patients with essential cryoglobulinemic vasculitis is of utmost importance as it has therapeutic consequences. A combination of antiviral treatment (interferon alpha with ribavirin) and immunosuppressive treatment (rituximab alone or with steroids, cyclophosphamide and even plasma exchange in very severe cases) has now been suggested [13].

Henoch Schönlein purpura (HSP) is a frequently occurring form of systemic vasculitis in childhood characterized by the deposition of IgA within the vessel wall [14]. Its etiology is unknown but its development or relapse has been described in conjunction with infections related to a multitude of micro-organisms. In a recent study on 55 pediatric cases with HSP, infection was considered a trigger for the disease in 29 patients [15]. These data need confirmation.

4. ANCA-associated vasculitides

The anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides comprise Wegener's Granulomatosis (WG), Microscopic polyangiitis (MPA) and its renal limited form, and Churg–Strauss Syndrome [2]. WG is strongly associated with antibodies to proteinase 3 (PR3-ANCA) and MPA with antibodies to myeloperoxidase (MPO) [16]. Several reports have suggested seasonal variation in presentation of these forms of vasculitis which may suggest microbial involvement [17]. However, specific micro-organisms have not been detected as causative agents in these diseases.

In WG, however, special attention has been given to *S. aureus*. Chronic nasal carriage of *S. aureus* occurs in around 63% of patients with WG in contrast to around 25% in healthy controls. Furthermore, chronic nasal carriage concurs with a strongly increased risk (relative risk of 7.2) for disease relapse [18] (Fig. 1). The mechanisms underlying this increased risk for relapse have not been clarified, but several hypotheses have been formulated [19]. First, superantigens from *S. aureus* may stimulate B- and/or T-cells. Indeed, in a second study, 82% (51 out of 62) of WG patients were chronic or intermittent carrier of *S. aureus* of whom 72.5% (37 out of 51) carried at least one strain positive for superantigens [20]. The presence of the toxic-shock-syndrome toxin-1 (TSST-1) superantigen was particularly associated with a strong risk for relapse (relative risk 13.3) [20]. Furthermore, T-cell activation was observed in patients with WG, even during quiescent phases of the disease [21]. However, the Vβ repertoire of expanded T-cells was not associated with carriage of specific *S. aureus* superantigens [22]. Mechanisms other than superantigen stimulation may be operative as well. *S. aureus* may activate B-cells polyclonally by cell-wall components of the bacterium. Such polyclonal stimulation may result in persistence of ANCA. Indeed, persistence of ANCA after induction of remission of WG, a strong risk factor for relapse, was related to chronic nasal carriage of *S. aureus* [18]. *S. aureus* may also directly prime neutrophils leading, amongst other, to surface expression of proteinase 3 (PR3), the target antigen of ANCA in WG. These primed neutrophils expressing PR3 can be fully activated by PR3-ANCA resulting in damage to tissues, especially vessel walls [16].

We have shown that cationic enzymes from *S. aureus*, in particular *S. aureus* derived acid phosphatase, bind to endothelial cells and localize also in glomeruli [23]. Antibodies to this phosphatase are present in patients with WG and may, thus, bind to *S. aureus* derived acid phosphatase deposited in the kidney. Indeed, the phosphatase was detected in 3 out of 19 renal biopsies from patients with WG. Furthermore, renal perfusion with the phosphatase in rats immunized with this enzyme resulted in severe necrotizing crescentic glomerulonephritis, the histopathological equivalent of renal lesions in WG [24].

Finally, a new mechanism based on the presence of complementary proteins and, possibly, related to *S. aureus* has recently been described [25]. In this study antibodies were described in patients with WG directed against complementary PR3, which is the protein translated from the antisense DNA strand encoding for PR3. In addition, the authors showed that immunization of mice with complementary PR3 not only induced antibodies to this protein but also to PR3 itself.

Table 3
Mechanisms by which *S. aureus* may induce or exacerbate Wegener's Granulomatosis

•Superantigens of *S. aureus* stimulate B- and/or T-cells
•Polyclonal activation of B-cells by cell-wall components of *S. aureus*
•Direct stimulation of neutrophils by *S. aureus* (priming!)
•Proteinases from *S. aureus* may bind α1-antiproteases resulting in persistence of active PR3
•Cationic enzymes from *S. aureus* may induce local vasculitis/glomerulonephritis resulting in severe disease in the presence of ANCA
•Peptides from *S. aureus* may induce, by molecular mimicry, antibodies to complementary PR3, which in turn via idiotypic–anti-idiotypic interactions, can induce PR3-ANCA

Interestingly, peptides from complementary PR3 show strong homology with peptides from *S. aureus*. So, peptides from *S. aureus* could, by molecular mimicry, induce antibodies to complementary PR3, which, in turn via idiotypic–anti-idiotypic interactions, could induce antibodies to PR3, the characteristic autoantibodies in WG. These data should be confirmed and extended.

So, in conclusion, carriage of *S. aureus* is seen in most patients with WG and is associated with persistent positivity for PR3-ANCA and relapsing disease. Various mechanistic explanations for this relationship are supported by experimental and clinical data (Table 3), but the exact way in which *S. aureus* modulates disease expression in WG needs further study.

The involvement of *S. aureus* in WG may also have therapeutic consequences. In a double-blind, placebo-controlled study patients received maintenance treatment with co-trimoxazole, 960 mg b.i.d., in order to test the hypothesis that this approach could reduce the occurrence of relapses in patients with WG. This treatment led to a strong decrease in the incidence of, mostly respiratory, infections. However, more importantly, the incidence of relapses decreased by 60% (relative risk 0.40) [26]. In a second study, patients with active limited WG, that is disease limited to the upper airways, received treatment with co-trimoxazole, 960 mg b.i.d., only without corticosteroids or immunosuppressives. Out of 31 patients, 18 reached complete remission and 9 patients partial remission after a median period of 3 months. However, 11 patients relapsed, at a median time of 14 months, particularly those patients not carrying *S. aureus* or with disease extending outside the ENT region (unpublished observation). These data also support a role for microbial agents in WG.

Take-home messages

- Infectious agents are probably involved in disease induction or disease expression in many cases of primary systemic vasculitis.
- Hepatitis C virus infection is associated with most cases of cryoglobulinemic vasculitis in Southern Europe but less frequently in Northern Europe.
- Hepatitis B virus infection in association with polyarteritis nodosa is decreasing in incidence.
- Chronic carriage of *Staphylococcus aureus* is a strong risk factor for relapse in Wegener's Granulomatosis.
- *Staphylococcus aureus* may exacerbate Wegener's Granulomatosis via different mechanisms.
- Monotherapy with co-trimoxazole is effective for patients with active Wegener's Granulomatosis limited to the upper airways, particularly when they are chronic carriers of *Staphylococcus aureus*.

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