Review

Infection and vasculitis

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Vasculitis may be associated with infection, immunization or anti-microbial drugs. Infections are responsible for a number of different types of vasculitis. Conversely, patients with vasculitis may develop infections, which sometimes mimic relapse. The aim of this review is to summarize the various aspects of the inter-relationship between vasculitis and infection, and the physiopathological mechanisms involved, in light of our current knowledge from animal models. Currently, a causal relationship between infection and vasculitis has only been established in a few instances and many mechanisms remain hypothetical. This inter-relationship is further assessed from the point of view of clinical presentation and therapeutic options, based on case reports and prospective observational data.

KEY WORDS: Infection, Vasculitis, Autoimmune, Immune mechanism, Animal model.

Introduction

The relationship between infection and vasculitis is complex [1]. Taking into consideration examples of historical diseases such as tuberculous or syphilitic aortitis, infections have long been suspected to be trigger factors for many types of vasculitis. However, a causal relationship has only been firmly established in a few instances using an epidemiological approach (e.g. PAN and HBV; cryoglobulinaemia and HCV). In most cases, however, this link remains hypothetical without formal evidence. The physiopathology of this inter-relationship remains poorly understood.

Animal models of vasculitis

Immune and autoimmune mechanisms are both responsible for vasculitis. Recently, antibodies such as ANCA and/or some key components of apoptosis have been found to be involved in the pathogenesis of various types of vasculitis in animal models. An important contribution to this field has been the use of a mouse model of ANCA-associated vasculitis [2]. Huugen et al. [2] used a model of passive transfer of anti-MPO antibodies prepared in MPO knock-out mice. They transferred the anti-MPO IgG to naïve C57BL/6 mice (control mice received anti-BSA antibodies). One hour after the administration of anti-MPO, bacterial lipopolysaccharide (LPS) was also injected intraperitoneally in some mice. Clinical manifestations (haematuria and leucocyturia) and pathological findings (necrotic crescentic glomerulonephritis) were more severe in mice receiving LPS, suggesting that LPS is an aggravating factor in anti-MPO vasculitis [2].

Some authors recently reported severe lung granulomatous vasculitis after intravenous injection of Fas ligand in a murine animal model [3].

There are also some other experimental animal models of vasculitis which suggest that infection could be a trigger in vasculitis and/or interfere with different immune mechanisms. These include parvovirus infection in Aleutian mink leading to vasculitis similar to human PAN, and epidemic equine coronavirus infection,

which is followed by endothelial infection with local inflammation and fibrinoid necrosis [4, 5].

Furthermore, when streptococcal toxins were injected into the ear arteries of rabbits, a vasculitic syndrome was induced [6]. Chlamydia pneumoniae was shown to induce aortic vasculitis in rabbits [7] and RNA virus and/or herpes virus produced aortitis and/or Behçet's disease in inbred mouse strains [8, 9].

Vasculitis of the great vessels has been described in mice lacking INF-γ responsiveness, and immunohistochemical studies showed that γ-herpes virus 68 infection in mice was followed by severe panarteritis [10]. However, although γ-herpes virus 68 has a high tropism for the media of the elastic arteries (a site that seems to allow the persistence of pathogens), this vasculitis is limited by IFN-γ [10].

Recently, Paessler et al. [11] described an animal model of eastern equine encephalitis. Infection of golden hamsters with eastern equine encephalitis virus, responsible for the most severe human arboviral diseases in the USA, resulted in histological findings of vasculitis with cerebral micro-haemorrhages similar to those described in humans.

Mechanisms of vasculitis

Several mechanisms could be involved in primary vasculitis related to infections [12, 13].

(i) A type III or immune complex reaction where the antigens are the infectious agents or antigenic portions of them [14]: after the zone of equivalence is reached, the immune complexes precipitate and become trapped within vessel walls, stimulating an immune response that leads to vascular injury.

Candida polysaccharides and fragments of Gram-positive and Gram-negative organisms can activate the alternate pathway and also lead to the inflammatory reaction characteristic of vasculitis [14–16].

Vasculitis resulting from the deposition of circulating immune complexes is represented by PAN associated with HBV infection, cryoglobulinaemia associated with systemic vasculitides, mainly the consequence of HCV infection, and HSP, which results from the deposition in the mesangium and vessels of IgA forming complexes.

Histology reveals mainly the deposition of immune complexes formed from viral antigens and from antibodies responsible for the activation of the classic complement pathway and for recruitment of neutrophils (i.e. PAN associated with HBV infection).

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Cryoglobulinaemia has been reported in HIV-1-infected patients [17], and considered to be associated with an increased death risk and/or neoplasia [18].

However, the production of circulating cryoglobulins does not seem to be related to HIV infection, but strongly correlates with HCV coinfection and liver cirrhosis [19].

Recently, features of cryoglobulinaemia vasculitis were studied in HIV and HCV coinfected patients. Therefore, coinfected patients had higher liver inflammation and higher gammaglobulinaemia, but lower cryoglobulin level [20]. Moreover, anti-HCV therapy was beneficial in this population [20].

Associated HIV infection significantly reduced the clinical and immunological expression of cryoglobulinaemia, except in coinfected patients with high viral loads for the both viruses [21].

Cryoglobulinaemia was further studied in coinfected patients in relation to their CD4 cell count by Aaron *et al.*, and resulting data suggest that cell-mediated immunity could contribute to the production of HCV-associated cryoglobulins [22].

(ii) Cell-mediated hypersensitivity: antigenic exposure may attract lymphocytes which liberate cytokines causing tissue damage and further activation of macrophages and lymphocytes (GCA).

In GCA for instance, the exposure to antigens (probably infectious, but no clear evidence supports this data) triggers a T-cell driven process leading to vasculitis. Dendritic cells from the vascular wall are potent antigen-presenting cells and therefore are able to activate $CD4^+$ T cells, which will be further responsible for macrophage and monocyte recruitment to the vessel wall [23].

These cells will release several cytokines (IL-1 and -6) and tissue-resident T cells release IFN-γ, which is a key pro-inflammatory cytokine that has been implicated in the pathogenesis of GCA. Sustained inflammation mediated by T cells, macrophages and the pro-inflammatory cytokines leads to intimal thickening and vessel occlusion. Platelet-derived growth factor and vascular endothelial growth factor also play important roles in the subsequent development of the lumen-occlusive arteritis.

(iii) Abnormal immune regulation (some vasculitis in HIV patients with advanced disease): in most vasculitis syndromes there is an abnormal expression of adhesion molecules and cytokines in vascular endothelium as a manifestation of an endothelial dysfunction that can be triggered by a variety of stimuli (including infectious agents, immune complexes and anti-endothelial cell antibodies).

(iv) Direct endothelial cell invasion can be the main pathogenic process in infections caused by CMV, herpes simplex, rickettsiae, fungi and bacteria [15, 16].

(v) Recent data suggest other mechanisms in the development of vasculitis within the context of infection [24]. Cytokines, such as TNF and various ILs, are produced directly by the stimulation from the infectious agents. Subsequently, recruitment of neutrophils to the small vessels occurs and leads to the development of vasculitis. Vasculitis related to infection due to streptococcus and staphylococcus has been associated with this mechanism of vascular injury.

Primary vasculitis and infection

PAN

PAN and its association with HBV is a classical example of primary vasculitis related to an infectious agent [25, 26]. There is no reliable animal model for PAN related to HBV, but virological and prevalence studies support a formal causality.

The association between PAN and HBV has been reported frequently (10−54%) [27–30], usually within the first 6 months after HBV infection. Over recent years there has been an important decrease in HBV-PAN [31], primarily due to HBV

TABLE 1. Infectious agents and PAN

Infectious agent	Frequency of association (references)	Supporting data
HBV	Strong [27–30]	Prevalence studies, virological
Streptococcus β-haemolyticus	Possible [33–35]	Anecdotal case reports
Klebsiella	Weak [36]	Anecdotal case reports
Pseudomonas	Weak [36]	Anecdotal case reports
Yersinia	Weak [37]	Anecdotal case reports
HIV	Weak [38–40]	Anecdotal case reports
Parvovirus B19	Weak [41, 42]	Anecdotal case reports
VZV	Weak [43]	Anecdotal case reports
Echinococcus	Weak [44, 45]	Anecdotal case reports
Trichinella	Weak [44, 46]	Anecdotal case reports
Ascaris	Weak [44, 45]	Anecdotal case reports

VZV: Varicella zoster virus.

vaccination and full pre-transfusional blood screening. Minor clinical differences have been noticed in HBV-PAN compared with non-infectious PAN including a dramatic onset, a milder favourable clinical course and seroconversion followed by complete healing. Biology in HBV-PAN reveals constant viral replication, HBsAg (7−36% of the cases) and inconstant immune complexes. Less than 10% of the cases of PAN are associated with HCV. In a retrospective study, important clinico-pathological features and therapeutic differences were found between HCV-PAN vasculitis and HCV-cryoglobulinaemia [32].

Some other infectious agents are reported in PAN, but without formal evidence data (Table 1).

A distinction should be done between PAN and HBV-related PAN, since there are important differences in pathogenesis with further consequences on treatment and prognosis.

INF-α and vidarabine used in a prospective, uncontrolled study resulted in improvements in survival and seroconversion in >50% of the cases [47]. Furthermore, Guillevin *et al.* [48, 49] demonstrated that short-term corticosteroids, plasma exchange and antiviral therapy in HBV-PAN were effective and safe.

Cryoglobulinaemia

The majority of the cases of cryoglobulinaemia are HCV related, and this link has been established since several years [50]. Further studies have shown that mixed cryoglobulinaemia is common in chronic HCV infection and is predominantly of type II [51]. Data from serological and virological investigations support a pathophysiological role for HCV infection in cryoglobulinaemia: positive anti-HCV testing (80−90% of the patients), circulating HCV-RNA, HCV in lesions and HCV-RNA in cryoprecipitate.

Furthermore, Sansonno *et al.* [52] have shown that HCV-RNA levels in circulating lymphocytes from patients with mixed cryoglobulinaemia are significantly higher compared with those observed in non-cryoglobulinaemic patients.

Recent data have identified the 1b HCV genotype as the genotype most frequently associated with cryoglobulinaemia, while genotypes 2–3 are associated with cryoglobulinaemia in coinfected HIV–HCV patients. The symptoms in cryoglobulinaemia related to HCV are mainly cutaneous, rheumatological and renal. However, there is no correlation between liver disease activity score and cryoglobulinaemia. The reported prevalence of cryoglobulins was 45.7% in HCV patients and the prevalence of symptoms associated with the presence of cryoglobulins was 27% [53].

Cryoglobulinaemia can also be secondary to HBV infection and the relationship between HBV and cryoglobulinaemia has been established since the detection of HBV in type III cryoglobulinaemia [54].

Levo [55] found HBV markers (HBsAg or its antibody) in cryoprecipitates in two-thirds (74% or 14/19) of their patients with mixed cryoglobulinaemia not related to lymphoproliferative disease or CTD. In serum specimens, 3 of the 25 sera were

TABLE 2. Infectious agents and cryoglobulinaemia

Infectious agent	Frequency of association	Supporting data
HCV	Strong [50–52]	Epidemiological, serological, virological
HBV	Possible [54, 55]	Epidemiological
HIV	Possible [18, 23]	Prevalence and virological studies Anecdotal cases
CMV	Weak [61–63]	Anecdotal cases
EBV	Weak [64]	Anecdotal cases
Parvovirus B19	Weak [59, 63, 65]	Anecdotal cases

TABLE 3. Infectious agents and WG

Infectious agent	Frequency of association	Supporting data
Staphylococcus aureus	Possible [69–71]	Serological, virological
Parvovirus B19	Weak [76, 77]	Anecdotal cases
Nocardia	Weak [78]	Anecdotal cases

TABLE 4. Infectious agents and KD

Putative aetiological agent	Frequency of association	Supporting data
Adenovirus	Weak [79]	Anecdotal
Herpes virus	Weak [80]	Anecdotal
Mycoplasma species	Weak [81]	Anecdotal
Toxigenic streptococci	Weak [82, 83]	Anecdotal
Toxigenic staphylococci	Weak [83–85]	Anecdotal
Propionibacterium acnes	Weak [86]	Anecdotal
Ehrlichia chaffeensis	Weak [87, 88]	Anecdotal
Rickettsia species	Weak [89, 90]	Anecdotal
EBV	Weak [91, 92]	Anecdotal
Retrovirus	Weak [93, 94]	Anecdotal
Human coronavirus New Haven	Weak [95]	Anecdotal
Measles virus	Weak [96, 97]	Anecdotal
Chlamydia pneumoniae	Weak [98, 99]	Anecdotal
Bartonella henselae	Weak [100]	Anecdotal
Coxiella burnetii	Weak [101, 102]	Anecdotal
Lactobacillus	Possible [103]	Experimental
Candida	Possible [104]	Experimental

positive for HBsAg (12%), and 12 had anti-HBV antibodies (48%) [55].

HBV and HCV have similar epidemiological characteristics, but the few cases of cryoglobulinaemia associated with HBV infection reported in the literature do not enable a determination of the precise role of coinfection with HCV [56].

In a series of 154 consecutive patients, the prevalence of cryoglobulins was found to be significantly higher ($P<0.001$) in HCV patients (46%) than in HBV patients (13.4%) [57].

Cryoglobulinaemia has occasionally been reported after HIV, CMV, EBV and parvovirus B19 infection, but there are only sporadic reports and no formal conclusion could be drawn [57–59] (Table 2).

A recent study in HIV-infected subjects however showed that this virus does not play an important role in the production of cryoglobulins [60].

In 1994, Misiani *et al.* [66] reported the benefits of INF-α *vs* no INF in a prospective, randomized, controlled trial: in the treated population, circulating HCV-RNA disappeared in 60% of the cases. Since the successful treatment of HCV-associated cryoglobulinaemic glomerulonephritis [67], a protocol combining IFN-α and ribavirin could be considered for HCV-cryoglobulinaemia. However, nowadays, some new therapies such as anti-CD20 monoclonal antibody administration are also discussed as treatment in these patients [68].

WG

Several data suggest an autoimmune and infectious pathogenesis in WG, a disease characterized by permanent T-cell activation: flare-ups are initiated by respiratory tract infections and circulating immune complexes [69], with the presence of granuloma [70]. Nowadays there is no clear evidence for an infectious trigger in WG, although several reports support that *Staphylococcus aureus* has a major role. The relationship between *S. aureus* and WG was first suggested by Wegener *et al.* and is supported by recent data. Stegeman *et al.* [71] demonstrated a strong association between *S. aureus* carriage and WG relapse, and selective reactivity of T-cell clones to *S. aureus* was reported. Prolonged administration of cotrimoxazole diminished relapse rates [72] and was efficient in cases unresponsive to other treatments, suggesting either an immunosuppressive effect via folic acid antagonism, or an infectious trigger for relapses [73].

Infections may play several roles in WG. Therefore, some mediators of inflammation such as TNF-α are locally released, inducing endothelial cell activation and neutrophil priming, and further ANCA-mediated PMN activation.

Cell-wall components of *S. aureus* represent powerful mitogens that can stimulate auto-reactive B cells to produce ANCA.

It has been suggested that *S. aureus* phosphatase acts as a 'planted' antigen and initiates glomerulonephritis and vasculitis [74].

In addition, microbial antigens may act as superantigens, causing selective expansion of T cells bearing particular TCR Vβ chain variable regions. Some authors reported abnormal expansion of T cells, using Vα and Vβ gene products, and other groups observed increased Vβ 2.1 gene usage in vasculitis.

However, a recent study [75] contests *S. aureus* superantigenic activity: despite production of superantigenic toxins by nasal carriage of *S. aureus*, there was no peripheral T-lymphocyte repertoire bias found.

In addition to *S. aureus* several other infectious agents have also been reported in WG, but without any consistent evidence (Table 3).

In the case of parvovirus B19-related WG, the main dilemma is whether this pathogen represents an aetiological agent or if it leads to opportunistic infection [76, 77]. The relationship between *Nocardia* and WG is also unclear. There is one reported case of *Nocardia* infection mimicking the WG triad [78], but also cases where *Nocardia* infection appeared during WG evolution, due to the immunosuppression present in this disease.

Kawasaki disease

An infectious aetiology has been suspected in Kawasaki disease (KD), based mainly on its epidemiological characteristics and clinical multisystemic presentation. Therefore, KD displays an age distribution similar to other childhood infections, and is more common in boys (male : female ratio 1.6 : 1) as observed in many infectious diseases where sex differences in immune responses are suggested to mediate susceptibility. Seasonal variation in KD incidence is observed in different geographical regions, and furthermore the clinical features of the disease are also characteristic of a severe acute childhood infection.

Al these epidemiological data could suggest an infectious aetiology for KD.

Several pathogens have been reported in this disease, but without any clear evidence for their contribution to pathogenesis (Table 4).

Laboratory techniques (microbiological, molecular and serological methods) were so far unable to identify an aetiological agent. Molecular techniques fail to detect circulating conserved microbial sequences in KD, suggesting either that the antigenic stimulus may arise from a distant site and/or may be a host-derived factor involved in the pro-inflammatory cascade.

However, the possibility of environmental factors influencing aetiology, possibly by modulating infection risk, remains, as suggested by some animal models.

Hence, it has been shown that microbial components from *Lactobacillus* and/or *Candida*, injected in animal models, induced coronary arteritis. Lehman *et al.* [103] immunized several mouse strains with intraperitoneal injection of *Lactobacillus* case cell wall extract (LCWE) and observed coronary arteritis 3 days after the immunization [103]. In a similar manner, *Candida albicans* water soluble fraction infused intraperitoneally in several mouse strains induced coronary vasculitis, associated with a high production of IL-6 and IFN-γ [104].

A superantigenic mechanism has been suggested, which may be related to an infectious agent, since KD shares many clinical features with superantigen-mediated diseases and has occasionally been reported concurrently in children with toxic shock syndrome, which is caused by superantigens [105]. Superantigens bind to the Vβ region of the TCR and clonal expansion of Vβ2-expressing T cells has been observed by some authors in KD [105], but this finding is inconsistent [106].

Duong *et al.* [107] used a similar model with LCWE but with genetically modified mice expressing human CD4 and human MHC Class II DQ6 transgenes in a background lacking endogenous CD4 and CD8. They observed that these mice displayed human-like responsiveness to bacterial antigens, and further *in vitro* studies have shown a superantigenic activity in the LCWE fraction that was directly correlated with the capacity of LCWE to induce coronary lesions. Furthermore, using the same animal model, Hui-Yuen *et al.* [108] reported that a TNF blocker (etanercept) could prevent the development of arteritis, suggesting the role of pro-inflammatory cytokines in the pathogenesis of KD.

Epidemiological and laboratory data supporting the infectious superantigenic hypothesis are lacking, although these data may reflect the involvement of as yet unidentified superantigen in humans [106].

Furthermore, a combined (antigenic and superantigenic) mechanism has been proposed [109].

Nevertheless, the pathogenic mechanisms in KD seem to be multifactorial, requiring certain immunological and genetic factors, and probably a vector.

Takayasu arteritis

Although the aetiopathogenesis of Takayasu arteritis (TA) is unknown, the increased number of activated circulating T cells and their localization in vascular lesions suggest that T cells are implicated in the initiation of the disease. Nevertheless, the putative trigger antigen(s) are still unknown. For long *Mycobacterium tuberculosis* has been thought to be a possible aetiological agent in TA but there is no convincing data for this, except one study [110].

Although several clinical studies were unable to find a correlation between infection and this vasculitis, some data concerning the implication of infectious agents in TA came from animal models. Fong *et al.* [111] and Laitinen *et al.* [112] reported aortic inflammation after *C. pneumoniae* infection, and observed bacterial antigen in intimal endothelial cells by immunohistochemistry.

RNA virus [porcine reproductive and respiratory syndrome virus (PRRSV)] and herpes virus were also found to induce vessel inflammatory lesions in pig and, respectively, mouse models. Rossow *et al.* [113] reported a multifocal systemic disease and Cooper *et al.* [114] renal vascular lesions after PRRSV infection. Several mouse strains infected with murine CMV (MCMV) disclosed aortic inflammation with mononuclear cells in the intima and adventitia, cytomegalic inclusion bodies in the smooth muscle cells and MCMV antigen on immunohistochemistry [115, 116].

Panarteritis with mononuclear infiltrates in the adventitia and media has been found in an IFN-γR$-/-$ mouse model after

TABLE 5. Infectious agents and TA

Infectious agent	Frequency of association	Supporting data
Mycobacterium tuberculosis	Possible [110]	Laboratory tests and anecdotal cases
Chlamydia pneumoniae	Possible [111, 112]	Experimental
RNA virus	Possible [113, 114]	Experimental
Herpes virus	Possible [113, 114]	Experimental
CMV	Possible [115, 116]	Experimental

TABLE 6. Infectious agents and GCA

Infectious agent	Frequency of association	Supporting data
Chlamydia pneumoniae	Possible [9, 119–121]	Serological
Parvovirus B19	Possible [9, 119–121]	Serological
Parainfluenza virus	Possible [9, 119–121]	Serological

infection with a γ-herpes virus, suggesting that IFN-γ plays an important role in virus-induced vasculitides [10] (Table 5).

Recent studies revealed a significant correlation between mHSP65 and hHSP60 reactive T cells as well as anti-mHSP65 and anti-hHSP60 IgG antibodies, suggesting an infection-induced autoimmunity in this disease, related to a potential molecular mimicry between mHSP65 and hHSP60 [117].

GCA

In GCA, vasculitis is mainly a T-cell driven process triggered by exposure to antigens (probably infectious). The sudden onset and variation in incidence between different geographical regions has led to the hypothesis that there is a genetic predisposition, correlated with environmental factors including infection, in this vasculitis. Infectious triggers have been searched for at the biological and epidemiological level. The pre-existence of clinical infections has been suggested in GCA, but without any epidemiological support, even though simultaneous peaks of GCA/PMR and respiratory infections have been reported [118].

Candidate pathogens in GCA, such as *C. pneumoniae*, parvovirus B19 and parainfluenza virus have been identified by PCR techniques [9, 119, 120] and/or serological tests [121].

For some authors, it seems that only reinfection with *Chlamydia* may induce vasculitis [122], but these data were not confirmed.

Various pathogens have been anecdotally reported in GCA including VZV, EBV, CMV, *C. psittaci*, *Borrelia burgdorferi* and *Treponema pallidum*, but without any serological or epidemiological basis (Table 6).

Behçet's disease

Behçet's disease is a chronic vasculitis of unknown aetiology. However, both viral and bacterial infections have been suspected to be involved in the pathogenesis of this disease [123]. *Streptococcus* species are suggested to play an important role in Behçet's disease. Stimulation with streptococcal antigens, as assessed by RT-PCR and ELISA, specifically increased expression of IL-12 p40 mRNA and protein, in conjunction with IL-12 p70 induction, in peripheral blood mononuclear cells from Behçet's disease patients [124].

Oral *Streptococcus* infections are classically reported in this form of vasculitis, but other pathogens have also been occasionally found (Table 7).

However, recently, parvovirus B19 DNA has been detected in the cutaneous lesions of patients with Behçet's disease [135]. Further progress in this field is being made using animal models of infection. For instance, Sohn *et al.* [136] has reported Behçet-like symptoms in ICR mice induced by HSV infection. However, recently, the same authors further suggest that viral infection

TABLE 7. Infectious agents and Behçet's disease

Infectious agent	Frequency of association	Supporting data
Streptococcus	Possible [123, 124]	Laboratory data
Staphylococcus aureus	Weak [125]	Anecdotal cases
Borrelia burgdorferi	Weak [126]	Anecdotal cases
Nocardia	Weak [127]	Anecdotal cases
Helicobacter pylori	Weak [128]	Anecdotal cases
Yersinia	Weak [129]	Anecdotal cases
Campylobacter	Weak [129]	Anecdotal cases
Salmonella	Weak [129]	Anecdotal cases
Chlamydia	Weak [129]	Anecdotal cases
HSV	Possible [130]	Experimental and anecdotal cases
Parvovirus B19	Possible [131, 135]	Case series and anecdotal cases
HAV	Weak [132]	Anecdotal cases
HBV	Weak [132]	Anecdotal cases
HCV	Weak [132]	Anecdotal cases
HEV	Weak [132]	Anecdotal cases
HIV	Weak [133]	Anecdotal cases
EBV	Weak [134]	Anecdotal cases

alone is not sufficient to induce Behçet's disease, and that immunological abnormalities are necessary [137].

Cogan's syndrome

Chlamydia species have been reported in Cogan's syndrome. In fact, five cases of vasculitis with serological findings indicating *C. pneumoniae* infection were reported by Ljungstrom *et al*. [138]. There are, however, no prevalence or microbiological studies, and no animal models that could support the correlation between Cogan disease and infection.

Vasculitis related to drugs

A large number of drugs, particularly antibiotics (β-lactams), can induce vasculitis which is mainly cutaneous. The incidence of antibiotic-induced vasculitis is probably underestimated, but drug-induced vasculitides are encountered more frequently than those secondary to infections. Among the drugs most frequently implicated have been sulphonamides, penicillin, allopurinol, thiazides, hydantoins, aspirin and propylthiouracil [139, 140]. Penicillin causes vasculitis by conjugating to serum proteins and mediating immune complex vasculitis as in type III hypersensitivity reactions [141].

Therapeutic agents from virtually every pharmacological class have been implicated in the development of drug-induced vasculitis [139, 140] and the mechanisms involved are mainly related to immune complex arterial deposits with antigen excess.

Drugs such as propylthiouracil and hydralazine appear to induce antibody production, specifically ANCA, although a clear cut causal relationship has not yet been proved [142].

The clinical spectrum of drug-induced vasculitis consists mainly of leucocytoclasic and hypersensitivity vasculitis, rarely necrotizing vasculitides, PAN-like, Churg–Strauss syndrome or cerebral vasculitis [143, 144]. Withdrawal of the drug is often followed by prompt resolution of clinical manifestations. However, some severe cases require corticosteroids, plasmapheresis, haemodialysis or cyclophosphamide, and death is reported in ~10% of the cases despite treatment. Sometimes systemic small-sized vessel vasculitis is described after massive antigen inhalation [145].

Several studies in animal models have shown that inhalation of soluble proteins through the respiratory tract leads to activation of $CD4^+$ 'helper' T cells. Exposure to aerosolized antigen appears to favour the generation of Th2 cells that secrete cytokines, predominantly IL-4, -5 and -13, which support the induction of humoral immunity [146].

Other authors have also identified a role for $CD8^+$ T cells after exposure to aerosolized proteins and these have been implicated in the control of airway hyperresponsiveness (AHR) through their capacity to secrete IFN [147].

Using scanning electron microscopy, Fischer *et al*. [148] and Moore *et al*. [149] have reported epithelial shedding and accumulation of inflammatory cells, expected signs of allergic airway inflammation, following inhalation of aerosolized antigen by immunized guinea pigs.

Anti-TNF treatments, even though a promising therapy for vasculitis, can sometimes induce a number of adverse effects, including vasculitis [150].

Therefore, recently, 39 cases of vasculitis during anti-TNF-α therapy were identified among 1200 French patients receiving this treatment [151].

A larger cohort of patients with autoimmune diseases has been reported between January 1990 and December 2006 after anti-TNF-α therapy by Ramos-Casals *et al*. [152] (233 cases, and among them 113 with vasculitis). Interestingly, in 25% of the cases the vasculitis had a systemic presentation, and in most of the situations the prognosis was poor, in spite of cessation of anti-TNF treatment [152].

Furthermore, due to their interference with the patient's immune system, anti-TNF and/or infliximab treatments are followed by an increased incidence of opportunistic infections, particularly tuberculosis [153], but also *Salmonella* and/or *Listeria* infections [154]. Other new therapies such as INF-α-2b also induce vasculitis [155].

Conclusion

The link between infection and vasculitis is an intriguing subject that has not yet been explored thoroughly. Vasculitis is associated with infections, immunization and anti-microbial drugs, and infections are reported during vasculitides and are presumed to be trigger factors. There are situations where one pathogen could be responsible for various types of vasculitis (e.g. HIV) and, conversely, where several micro-organisms could induce the same vasculitic syndrome (PAN).

However, in most of these instances, data come from only a few sporadic case reports and a firm conclusion linking the infectious agent to the pathogenesis of vasculitis cannot be drawn. A causal relationship between infection and vasculitis has been proven in only few situations (HBV and HCV in PAN and cryoglobulinaemia, respectively). The physiopathology of the complex relationship between infection and vasculitis is not understood completely, but new molecular tools should allow a better understanding of the mechanisms underlying these pathologies and may offer a different therapeutic approach in the future.

Rheumatology key messages

- Infections are responsible for different types of vasculitis, but in most cases this link remains hypothetical.
- A causal relationship has only been established in few instances (PAN, HBV, cryoglobulinaemia and HCV).
- Several mechanisms could be involved in primary vasculitis related to infections.

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Clinical Vignette

Peridental mass in a patient with Forestier's/DISH

A 73-year-old man presented with paresthesias and weakness in the upper extremities. No evidence of joint inflammation or neurological deficit of the lower extremities was present. MRI of the cervical spine revealed a soft tissue pannus mass about the dens process impressing on the spinal cord (Fig. 1). Diffuse idiopathic skeletal hyperostosis (DISH), Forestier's disease, with secondary fusion below C2, was found to be the underlying aetiology. While the differential diagnosis of a peridental mass with cystic lesion at the C1–C2 levels includes arachnoid, fibrous, ependymal, teratomatous, perineural and meningial cysts, peridental masses have also been detected in patients with rheumatic conditions. Patients with RA with dens erosions and subaxial cervical instability, CPPD with dens involvement ('crowned dens') and synovial cysts of the spine have been reported. Very few patients with peridental masses and DISH have been reported, and only in the neurosurgical literature [1]. These masses may develop in such cases due to enhanced mechanical stress at C1–C2 as the only mobile joint, due to fusion below C2 secondary to DISH. Our patient underwent neurosurgical decompression and C1–C2 Harm's fusion, with neurological improvement and disappearance of the peridental mass on repeat MRI.

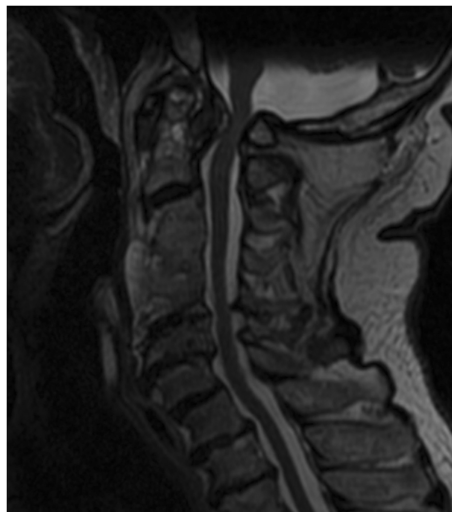*Disclosure statement*: The authors have declared no conflicts of interest.

FIG. 1. MR imaging findings in a 73-year-old man with DISH. T2-weighted sagittal MR image shows pannus formation at the craniocervical level and C1–C2 articulation causing severe compression of the medulla oblongata and spinal cord. The hyperintensity within the cord indicates myelopathy. Note the vertebral body fusion at C3-C4-C5 levels.

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