Overview of infections as an etiologic factor and complication in patients with vasculitides

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Abstract

Vasculitides, a form of inflammatory autoimmune disease targeting the vessels, constitute an entity with significant morbidity and mortality. Infections have long been associated with vasculitides as a result of the incident immunosuppression following treatment induction and maintenance. Several microbial pathogens have been described as etiologic factors of infections in this patient population according to the type of vessels affected. Intense research has also been recently conducted in the interplay between vasculitides and certain viral infections, namely human immunodeficiency virus and severe acute respiratory syndrome coronavirus 2. Of note, a plethora of scientific evidence is available regarding the role of infections as triggering factors for vasculitides. Among the main mechanisms implicated in this direction are the activation of B and T cells, the direct endothelial insult, the immune complex-mediated vascular injury, and the cell-mediated, type IV hypersensitivity vessel damage. Therefore, this review aims to summarize all the available evidence concerning this bidirectional interplay between infections and vasculitides.

Keywords Vasculitis · Infection · COVID-19 · HIV

Introduction

Vasculitides are a heterogeneous group of autoimmune diseases with great morbidity and mortality, characterized by fibrinoid necrosis and the presence of inflammatory leukocytes, leading to damage of the vessel wall [1]. Inflammation in this patient population leads to narrowing or even obstruction of the vessels resulting in reduced blood perfusion and the development of ischemic damage to the tissues and organs.

Both the size of the vessels and the organs affected are different between the different types of vasculitis and, therefore, their clinical manifestations vary [1]. Vasculitides may be pronominally classified into large-, medium-, and small-sized vessel vasculitides, as well as into primary or secondary vasculitides, including infectious or paraneoplastic vasculitides. In this review article, we first provide the latest

evidence regarding the association between infections and vasculitides in an effort to increase awareness of the infectious etiology of vasculitis.

Search strategy

We performed a literature search in PubMed, Google Scholar, and Web of Science from inception till 15th January 2022, using the following keywords: vasculitis, infection, bacterial infection, viral infection, coronavirus disease-19, COVID-19, SARS-CoV-2, human immunodeficiency virus, HIV. Additionally, articles were extracted from the reference list of the retrieved articles if they were deemed relevant. Specifically, we focused our attention on papers published within the last 5 years.

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Evidence for the relationship between infections and vasculitis

In the past, historical diseases such as tuberculosis or syphilitic aortitis have long been suspected to be triggering factors for many types of vasculitis [2].

Many different types of vasculitides may be associated with infections (Table 1). On the other hand, patients with vasculitis may develop infections, which sometimes mimic a relapse of the disease.

When an infection has been diagnosed in a patient with vasculitis, the subsequent question is to determine whether vasculitis is related or not to the infection and how to treat both conditions in the most appropriate and safest ways [10, 22, 23]. So far, a causal relationship between infection and vasculitis has only been established in a few instances, and the pathophysiologic mechanisms remain hypothetical [2].

Type of vasculitis and different infectious agents involved

In the small-vessel vasculitis, including ANCA-associated vasculitides (AAV) [24, 25] and/or small-vessel, immune complex-mediated vasculitis [4, 5, 11], the possible role of infection in triggering de novo disease and relapse has been extensively investigated and a clear association has been demonstrated. On the other hand, there is only indirect evidence to support an infectious etiology for Kawasaki's

disease, even though numerous organisms have been proposed but not proven [26].

In patients with granulomatosis with polyangiitis (GPA), *S. aureus* was the most commonly isolated organism in cultures from the upper airways that have been associated with an increased risk of relapse [24]. In light of this evidence, a cyclical pattern of GPA occurrence in cases of an infectious etiology is supported and is exhibited periodically with a maximum peak every 7.7 years [25].

Moreover, microscopic polyangiitis (MPA) is also associated with infections and environmental factors. It is suggested that infection is a major causal factor in the formation of ANCA. Importantly, substantial differentiation of glomerulonephritis due to infection and immune complex deposition versus ANCA-associated vasculitis could be easily performed with a kidney biopsy [6]. Indeed, different case reports have been described, whereby infective endocarditis caused by *E. faecalis*, *Streptococcus*, and *Bartonella* species were also related to ANCA vasculitis and markedly elevated levels of PR3-ANCA [6].

On the contrary, in the setting of eosinophilic granulomatosis with polyangiitis (EGPA), the majority of cases are idiopathic, associated with inhaled antigens rather than infections. Herein, vaccination and desensitization have been reported as triggering factors [27]. However, in EGPA the epidemiological data may be confounded by the severity of preceding asthma [28].

In IgA vasculitis-Henoch-Schonlein purpura (HSP), it is suggested that infections can trigger immune complex

Table 1 Microbial etiology for induction or exacerbation of vasculitis

Study	Mechanisms	Type of infection	Type of vasculitis
Bacteria [3–9]	Direct invasion or Immune complex-mediated	<i>Mycobacterium</i> TBC Non-TBC mycobacterial <i>S. aureus</i> <i>Streptococcus</i> Gram-negative Rickettsia <i>Pseudomonas aeruginosa</i>	Syphilitic aortitis GPA HSP Leukocytoclastic vasculitis Cutaneous vasculitis
Virus [10–16]	Direct endothelial Invasion or Indirect autoimmune mechanisms ↓ by immunological factors or by direct vascular injury	HBV HCV HIV HTLV-1 Erythrovirus B19 CMV VZV	PAN Cryoglobulinemic Vasculitis Giant cell arteritis HSP
Fungi [17]	Direct invasion or Septic embolism		Mycotic aneurism
Parasites [18–21]	Direct invasion	Toxoplasmosis Trichinosis Toxocariosis	Cutaneous Vasculitis

TBC tuberculosis, *GPA* granulomatosis with polyangiitis, *HSP* Henoch-Schonlein purpura, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HIV* human immunodeficiency virus, *HTLV-1* human T-cell lymphotropic virus type 1, *PAN* polyarteritis nodosa, *CMV* cytomegalovirus, *VZV* varicella-zoster virus

deposition. Although long-term observations are lacking, an interesting concept was presented as patients exhibited a constantly increased risk for serious infections during follow-up. Additionally, a higher rate of upper respiratory tract infections has been shown [3]. Concerning children with IgA vasculitis, specific inflammatory factors may be attributed and have a lasting effect on immune competence [4]. Another point of importance is that the incidence of IgA vasculitis exhibited seasonal increases in the spring and decreases in the winter, which may be related to a higher frequency of upper respiratory tract infections during the coldest months of the year. Interestingly, in the majority of patients with HSP there is an infection of the upper respiratory tract, indicative of a potential microbial etiology of the disease. Among children aged less than 10 years, 99.5% of cases suffer from either IgA vasculitis or Kawasaki disease, both exhibiting a seasonal pattern paralleling infections [29]. IgA vasculitis has also been associated with influenza infection [11].

Last but not least, leukocytoclastic vasculitis may also be a manifestation of bacterial infection [5]. Etiologically, the appearance of small-vessel cutaneous vasculitis is associated with drug reactions or certain viral or bacterial infections. Among patients with cutaneous vasculitis, beta-lactams, analgesics, or non-steroidal anti-inflammatory agents are common drugs associated with the disease, which usually have a good clinical outcome [30]. In leukocytoclastic vasculitis, the presence of upper respiratory tract infections shortly before the development of vasculitis was more common than in those with IgA vasculitis [5]. Cutaneous vasculitis has been described in patients with cystic fibrosis due to respiratory infections due to *Pseudomonas aeruginosa*, *S. aureus*, *Haemophilus influenza*, and *Burkholderia cepacia* complex [8, 31, 32]. Furthermore, a cutaneous small-vessel vasculitis may occur in childhood after an infection caused by the atypical bacterial pathogen *Mycoplasma pneumoniae* [33].

Hepatitis B virus-associated polyarteritis nodosa

Polyarteritis nodosa (PAN), a medium-vessel vasculitis, frequently results from hepatitis B virus infection (HBV-PAN). HBV-PAN has become the most convincingly documented, immunologically-mediated, infection-associated systemic vasculitis and the single most important feature in confirming the diagnosis of PAN [13]. One of the highest rates reported comes from an area endemic for HBV infection and accounts for 30% to be HBV positive [34]. Control of the viral infection is mainly based on the use of antiviral drugs with the current availability of potent agents. Other rare cases of PAN have been associated with nontuberculous mycobacterial infection [14], with cutaneous polyarteritis

nodosa occurrence in the setting of *Mycobacterium tuberculosis* infection also being described [35].

Hepatitis C virus-associated cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis is the most frequent extrahepatic manifestation in patients infected with the hepatitis C virus (HCV) [10]. This causative relationship between hepatitis C and cryoglobulinemic vasculitis is well-established in more than 80% of the patients [12]. Its incidence has decreased over the past few decades, with direct-acting antivirals not always effective at eradicating or preventing the relapse of this complication despite achieving a sustained viral response [36–38].

Human immunodeficiency Virus-associated vasculitides

Human immunodeficiency virus (HIV) positive patients may also develop vasculitis, either mediated by immunological factors or by direct vascular injury, as well as by the restoration of protective pathogen-specific cellular immune response owing to the immune restoration inflammatory syndrome induced by antiretroviral treatment [39]. Hypersensitivity reactions should be considered as a possible etiology of vasculitis in HIV-infected patients [40]. HIV-associated PAN-like disease and Kawasaki-like syndrome have also been described, with significant differences when compared to the classic manifestations of PAN and Kawasaki disease, respectively [39]. Regarding large vessel vasculitis, it is more commonly encountered in HIV patients at an advanced disease stage, with multiple aneurysms and occlusions in less typical locations, sharing histologic similarities with Takayasu arteritis [41]. It should be noted that this large vessel vasculitis occurs independently of CD4 count and viral load, as well as in patients after starting antiviral therapy indicating the immune reconstitution inflammatory syndrome (IRIS) [42]. Physicians should be aware that vasculitis may have a heterogeneous presentation and can occur in association with HIV infection [15].

Coronavirus disease-19-associated vasculitides

The role of the recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), characterized by an inflammatory cytokine storm and incident endotheliitis [43, 44], in the pathogenesis of IgA-mediated vasculitis needs to be determined. Recently the occurrence of Henoch-Schönlein purpura secondary to a SARS-CoV-2 infection in children and adults was mentioned in several case reports [45]. Since SARS-CoV-2 causes a mucosal infection, the incident IL-6 production might be responsible for the

stimulation of poor glycosylation/galactosylation of IgA1, leading to the formation of galactose-deficient IgA1, thus contributing to IgA vasculitis development and progression [46]. Case reports of AAV following coronavirus disease-19 (COVID-19) have also been described, presenting with renal involvement and contrasting prognosis [47]. Moreover, COVID-19 has been linked with the manifestation of other forms of vasculitis, such as Kawasaki disease and leukocytoclastic vasculitis [48–50]. SARS-CoV-2 may also lead to a small vessel vasculitis not involving the main coronaries [51]. Evidence of central nervous system vasculitis following COVID-19 was confirmed via biopsy despite a mild form of SARS-CoV-2 infection [52]. Gracia-Ramos et al. reviewed the available evidence on the incidence of autoimmune diseases in COVID-19 patients [53]. In incidence vasculitis patients, they noted a male sex predisposition, with the majority of patients exhibiting a mild-to-moderate COVID-19 disease course [53]. Vasculitis onset was reported approximately one month after SARS-CoV-2 infection and completely resolved in the vast majority of cases [53]. In a recently reported positron emission tomography/computed tomography study of recovered adult COVID-19 patients with residual symptoms, a higher target-to-blood pool ratio was observed in the thoracic aorta, right iliac artery, and femoral artery of COVID-19 patients compared to control, indicating a persistent vascular inflammation which could be responsible for vasculitic manifestations in the long-term recovery period [54]. AAV may as well be a complication of the Long-COVID-19 syndrome, with deleterious outcomes [55].

In children, Multisystem Inflammatory Syndrome (MIS-C) is a newly defined post-viral myocarditis inflammatory vasculopathy following COVID-19 infection [56], which can be complicated with giant coronary aneurysm formation [57]. Importantly, this syndrome differs in several aspects (epidemiology, clinical, and immunological findings) from Kawasaki disease [58]. This syndrome can also be found in adult patients (MIS-A), usually four months after the acute phase of COVID-19, presenting with multiorgan dysfunction frequently requiring intensive care unit admission, while a minority of patients may present with Kawasaki disease [59]. It should be stressed, however, that prompt immunomodulatory treatment may lead to the regression of myocardial injury and the reversibility of left ventricular dysfunction [60].

Further research in this field is required, however, to better define the pathophysiologic basis of autoimmune diseases incidence in COVID-19 [61]. It should also be stated that vaccination against SARS-CoV-2 may also be complicated with cutaneous vasculitic phenomena or even IgA vasculitis and AAV [62–66].

Other virus-associated vasculitides

Human T-cell lymphotropic virus type 1 (HTLV-1) has been shown to infect human endothelial cells and may explain the CNS vasculitis associated with the progressive spastic paraplegia seen with HTLV-1 infections [67]. Other viruses such as Erythrovirus B19, cytomegalovirus, and varicella-zoster virus have also been reported to be associated with or implicated in the development of vasculitides [10]. Additionally, norovirus infection can precipitate the worsening of an underlying HSP vasculitis and lead to acute clinical decompensation [68].

Fungal and parasitic disease-associated vasculitides

Fungi diseases can also cause vasculitides. Herein, the proposed mechanism involves the direct invasion of blood vessels or septic embolization, leading to the well-known feature of ‘mycotic aneurysm’ [17]. It is noteworthy that various induction therapies in AAV also result in opportunistic fungal infections [69].

A plethora of parasitic diseases has been associated with vasculitis. Toxoplasmosis, trichinosis, strongyloidiasis, ascariasis, sarcocystosis, amoebiasis, leishmaniasis, and toxocarasis have been anecdotally reported in conjunction with vasculitis with cutaneous and/or systemic manifestations [18–21, 70].

Mechanisms of infection-associated vasculitis

Studies have provided valuable information on the mechanism of inflammation and innate immunity (Fig. 1). The mechanisms of infection-related vasculitis involve direct and indirect pathogen invasion. Direct pathogen invasion is detected within the blood vessel walls and is characterized by smooth muscle cell (SMC) accumulation, endothelial dysfunction, expression of reactive oxygen species (ROS), cytokines, chemokines, cellular adhesion molecules, and damage of the vessel wall [71]. It is also suggested that the pathogenesis of vasculitis differs according to the pathogenic organisms. The indirect mechanisms of infection-related vasculitis involve immune-mediated injury to the vessel walls, such as immune-complexes molecular mimicry, ANCA, cytokines, superantigens, autoantigen complementarity, and T cell immune response [71].

Activation of T and B cells

Infections stimulate autoimmune responses with shared epitopes between pathogens and host, upregulated heat shock proteins, and stimulated lymphocytes [22]. Circulating

Fig. 1 Mechanisms of interactions between infections and vasculitides consist of either a direct invasion of endothelial cells by the pathogen leading to vascular injury or indirectly by the activation of T and B cells, immune complex-mediated, or cell-mediated vessel damage

toxins often act as superantigens which are exotoxins produced by a small group of bacteria, primarily *S. aureus* and *Streptococcus pyogenes* [72]. These induce oligoclonal activation of T cells through an antigen-independent mechanism [73].

Superantigens also stimulate B cells to produce autoantibodies that may be involved in the pathogenesis of vasculitis (Fig. 2, Panel a) [22, 23]. The ‘classic neutrophil pathway’ has been described as a cause of necrotizing vasculitis and has been studied and confirmed by several groups. An additional ‘T-cell pathway’ has also been proposed, mainly causing granulomatous inflammation, promoting necrotizing vasculitis [74]. Infections are the starting point of both pathways and trigger the priming of neutrophils [74].

Immune complex-mediated damage

Immune complex-mediated damage represents a reaction of type III hypersensitivity where the antigens are the infectious agents or antigenic portions of them after the zone of equivalence is reached. The immune complexes precipitate and become trapped within vessel walls, stimulating an immune response (Fig. 2, Panel b) [75]. Type III hypersensitivity produces soluble immune complexes and, under certain conditions, may occasionally produce devastating tissue damage. A disease caused by soluble immune complexes may also be due to autoimmunity when the antigen involved is self-derived. Studies of circulating complement levels have shown a correlation with disease activity [75].

Defective handling of antigenic peptides, whether due to high antigenic load or abnormally functioning immune

regulatory mechanisms, in chronic viral infections such as hepatitis C or hepatitis B, might contribute to a state of persistent antigenemia, stimulation of an immune response with subsequent release of antigen-directed antibodies, and the formation of immune complexes. Subsequent complement activation generates the chemotactic factor C5α, which promotes the accumulation of circulating neutrophil and monocytes-macrophages [76]. It has been proposed that factors released by ANCA-activated neutrophils activate the alternative pathway of complement, resulting in enhanced recruitment and activation of neutrophils [77]. The alternative pathway is activated by a variety of cellular surfaces, including those of certain bacteria, viruses, fungi, and parasites. Sequential non-enzymatic protein–protein interactions among the terminal complement proteins initiated by C5a lead to the formation of the membrane attack complex (MAC). Because biological activities of C5a and MAC play a role in the pathogenesis of endothelial injury, this alternative pathway is now considered pathogenically important, and complement inhibitors (such as anti-C5a) may have efficacy in AAV, with C5a potentially being an important therapeutic target [78]. Immunosuppressive therapy with glucocorticoids underpins current treatment for AAV. Agents targeting the complement system such as eculizumab, a monoclonal antibody that prevents the formation of C5a and C5b-9, and avacopan, a small molecule inhibitor of C5aR, may represent an alternative to steroids [9, 79].

Neutrophils are required for the development of bacteria-associated vasculitides. They can sometimes be attributed to an antigen excess which in turn causes a rise in circulating immune complexes and inflammatory mediator deposition

Fig. 2 Differential pathophysiologic pathways of infection-associated vasculitis. **a** Activated B cells, T cells, and superantigens in the setting of infection may lead to vessel injury. **b** Complement activation and the formation of immune complexes, a form of type III hypersensitivity, leads to increased vascular permeability and inflammation. **c** Endothelial cell invasion by bacteria could also promote endothelial dysfunction and vasculitis. **d** A cell-mediated, type IV hypersen-

sitivity reaction with the attraction of lymphocytes to antigens may promote tissue damage and macrophage activation, with an abnormal expression of vascular adhesion molecules and cytokines. *MC* monocyte, *ICAM-1* intercellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *P-S* P-selectin, *E-S* E-selectin, *TNF- α* tumor necrosis factor- α , *IL* interleukin

within the vessel walls, with subsequent complement activation and blood vessel wall damage [75].

Direct invasion of the endothelial cells

Vasculitides following bacterial infections may occur from direct invasion of the endothelial cells as a result of an extension of a localized focus of infection affecting blood vessels or due to blood-borne septic embolization (Fig. 2, Panel c) [80].

Direct necrotizing vessel wall destruction can be induced by *Pseudomonas aeruginosa* or *Legionella pneumophila* in the lungs or *Fusobacterium necrophorum* in the internal jugular veins after pharyngitis [80]. In addition, fungi, protozoa, and helminths usually cause vasculitis through direct invasion of the vessel walls. Several bacteria, including *Pseudomonas aeruginosa*, *S. aureus*, *Burkholderia cepacia*, *L. monocytogenes*, and *Haemophilus influenza*, have been incriminated [6]. Direct endothelial cell invasion can also be the main pathogenic process in infections caused by CMV and herpes simplex virus [80]. A study reported that intracerebral varicella-zoster virus (VZV) antigens and DNA could be isolated from the walls of temporal arteries of a

large proportion of patients affected with giant cell arteritis or aortitis [16].

Cell-mediated hypersensitivity type IV

Antigenic exposure may attract lymphocytes which liberate cytokines causing tissue damage and further activation of macrophages and lymphocytes (Fig. 2, Panel d) [81]. The abnormal expression of adhesion molecules and cytokines in vascular endothelium in most vasculitis syndromes as a manifestation of endothelial dysfunction can be triggered by a variety of stimuli, including infectious agents, immune complexes, and anti-endothelial cell antibodies [2].

Infections in immunosuppressed patients with vasculitis

The interest in infection-related vasculitides has been boosted over the last 2 decades by the development of new molecular techniques and the proof of true associations between viral infections and systemic vasculitis [82]. The aggressive treatment of vasculitis incurs a variety of adverse effects, among which infection is the most common and

prevailed as a major complication in every stage of vasculitis. In long-term follow-up studies, the incidence of infection was approximately 30% [7]. Most of the infections occurred during the first six months of vasculitis onset with high mortality [7]. Each type of vasculitis perhaps is associated with different infectious agents. Infections in vasculitides can be further divided into categories according to the infective agents: bacteria, fungi, and viruses [7].

Bacteria are the main infectious agents, accounting for 75.9% of all the cases [7, 22]. Gram-negative bacteria were the leading causative agents. Mixed infection was also noticeable. The distribution of infective sites includes primarily the lungs and the skin [7]. Opportunistic infections like *Pneumocystis jirovecii* pneumonia (PJP) occur early in the course of AAV, and it is frequently associated with the induction of immunosuppression [83]. However, PJP is not limited to the first six months following AAV diagnosis, and late-onset infection can occur in the context of augmented immunotherapy, particularly with concurrent lymphopenia [83]. It should be noted that AAV treatment with rituximab has been associated with a high frequency of bacterial infections in a recently reported meta-analysis [84]. At the same time, prophylaxis with trimethoprim-sulfamethoxazole may be associated with a lower risk of bacterial infections in this subgroup of patients [85].

Risk factors for infections in vasculitides

In a recent study, risk factors for infection in patients with vasculitis at the time of the diagnosis included age, smoking, kidney dysfunction, low CD4 counts, and cyclophosphamide (CYC) therapy [17]. Other factors associated with infection in patients with vasculitis included dialysis dependence, anemia, and hypoalbuminemia [7]. Interference with cell-mediated immunity, particularly with low CD4 counts, predisposes to infections [86]. Thus, close monitoring of lymphocyte counts could improve the prognosis of patients with vasculitis with regard to infection incidence [7]. It is now apparent that prophylaxis should be considered for other patients who are receiving intense immunosuppressive therapy, especially if they are lymphopenic or have a low CD4 count [69].

With regards to factors predisposing to a worse prognosis in patients with systemic vasculitis and COVID-19, important insight was provided by the latest retrospective cohort study (1202 patients), with 49.8% of patients requiring hospitalization [87]. Of the hospitalized patients, approximately 22% died. Poor COVID-19 outcomes were seen in older male subjects [87]. Moreover, the presence of an increasing number of comorbidities was related to an adverse COVID-19 prognosis, while at least moderate vasculitic disease activity and the intake of 10 mg/day of prednisolone led to a higher odd of COVID-19 severity and

mortality [87]. Moreover, the presence of comorbid respiratory disease might represent an additional risk factor, as shown by Rutherford et al. in a multicenter cohort of 65 patients with systemic vasculitis and COVID-19 [88].

Immunosuppressive agents and infections in vasculitides

The rate of severe infections and infection-related mortality in patients with severe vasculitis treated with immunosuppressive agent induction therapy was high. A recent meta-analysis including four studies and a total of 888 subjects estimated that in randomized controlled trials of necrotizing vasculitis, GPA, MPA, EGPA, and PAN treated with CYC combined with high dose glucocorticoids (GC) (mean cumulative doses of CYC were 2.7–50.4 g and of GC were 6–13 g), the risk of severe infection was 2.2%, the risk of any infection was at 5.6%, and an infection-related death was estimated at 1.7% per year per gram of CYC [23]. Interestingly, age, serum creatinine, and cumulative GC dose were not significantly associated with the rate of severe infections [23]. It is also suggested that oral CYC, which had a higher cumulative CYC dose compared to intravenous CYC, showed lower infection rates [89].

As far as rituximab therapy is concerned, a considerable percentage of patients with AAV may be susceptible to severe infections, with increasing age, impaired renal function, and lower body mass index acting as risk factors [90, 91]. Dosing regimens (four-dose and two-dose) do not differ in the rate of incident infections [92]. In a recently reported Bayesian network meta-analysis of randomized controlled trials, mycophenolate mofetil was likely the safest treatment option with regard to severe infections in patients with AAV, followed by CYC, azathioprine, rituximab, and methotrexate [93]. The differences, however, were marginal and the only statistically significant comparison involved mycophenolate mofetil and methotrexate [93]. A combination of immunosuppressants (rituximab, CYC, GC) was not associated with a higher rate of severe infections in a cohort of patients with life-threatening AAV [94]. However, high-dose GC added to rituximab may be related to a greater incidence of severe infections in a randomized clinical trial of patients with AAV but without severe glomerulonephritis or alveolar hemorrhage [95]. At the same time, the low-dose GC regimen was non-inferior regarding disease remission induction at six months [95].

COVID-19 in patients with vasculitides

The impact of SARS-CoV-2 infection and COVID-19 in patients with preexisting vasculitis also deserves an honorable mention. The presence of vasculitis was associated with 1.6-fold higher odds of hospitalization, while the use

of disease-modifying anti-rheumatic drugs did not affect the need for hospitalization [96]. In the retrospective cohort study by Sattui et al. approximately 50% of patients required hospitalization and 15% died [97]. Among the identified risk factors were the increased age, male sex, comorbidity burden, and high-dose glucocorticoids [97]. Similar risk factors were proposed by the results of the COVID-19 Global Rheumatology Alliance physician-reported registry of patients with rheumatic diseases and confirmed or suspected SARS-CoV-2 infection, where the use of rituximab, sulfasalazine, and other immunosuppressants (azathioprine, cyclophosphamide, ciclosporin, mycophenolate, or tacrolimus) was additionally linked to increased death rates compared to methotrexate monotherapy [98]. Interestingly, the use of anti-tumor necrosis factor (TNF) agents was associated with a decreased odds of hospitalization [96]. Additionally, the use of the monoclonal antibody bamlanivimab was proven efficacious in a small cohort of patients with COVID-19 and AAV on rituximab therapy [99], a subgroup characterized by an impaired immune response to SARS-CoV-2 vaccination [100]. However, a booster dose may be met with greater success in these patients and is, therefore, warranted [101]. It is also worthwhile mentioning that vaccination against SARS-CoV-2 is well-tolerated and generally safe in patients with inflammatory rheumatic diseases, including vasculitides, with low rates of breakthrough infections [102]. However, disease relapses have been reported in patients with AAV and HSP [103, 104]. Finally, the impact of the pandemic in patients with vasculitides may be indirect through the interruption of immunosuppressive treatment, subsequently leading to increased rates of disease flares [105].

Conclusions

The relationship between infection and vasculitis is complex. Infections have long been suspected to be triggering factors for many types of vasculitides. A causal relationship has only been firmly established in a few instances using an epidemiological approach. Of great importance is the recognition of the infectious origin of vasculitides. Treatment strategies differ from those applied to non-infectious vasculitides. A high index of suspicion is required because clinical features are not always specific. Thus, an infection should always be excluded based on appropriate examinations, and, if confirmed, early and aggressive treatment should be administered. This accurate etiological diagnosis is important since immunosuppressive treatment may lead to further deterioration if an infection is the cause of vasculitis. Moreover, vasculitides and the need for immunosuppression represent a major risk factor for the development of common and opportunistic infections, including the highly prevalent SARS-CoV-2, which may additionally hinder the prognosis

of these patients. Therefore, their prompt recognition and treatment are of utmost importance in this patient population to prevent excess morbidity and mortality.

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