**Vasculitides secondary to infections**

C. Pagnoux, P. Cohen, L. Guillevin

**ABSTRACT**

Many viruses can be responsible for systemic vasculitis, the most frequent being hepatitis B virus-related polyarteritis nodosa (HBV-PAN), even though its incidence has decreased over the past few decades. Mixed cryoglobulinemia has been shown to be associated with hepatitis C virus (HCV) infection in more than 80% of the patients, but it remains asymptomatic in most of them with only a minority developing vasculitis. Human immunodeficiency virus (HIV), erythrovirus B19, cytomegalovirus, varicella-zoster virus, and human T-cell lymphotropic virus-1 (HTLV-1) have also been reported to be associated with or implicated in the development of vasculitides. On the other hand, some bacteria, fungi or parasites can also cause vasculitis, mainly by direct invasion of blood vessels or septic embolization, leading, e.g., to the well-known feature of 'mycotic aneurysm'. Syphilitic aortitis and/or cerebrovascular disease and rickettsial diseases are other, more specific, bacteria-induced vasculitides. Recognizing an infectious origin of vasculitides is of great importance because treatment strategies differ from those applied to non-infectious forms. Effective antimicrobial drugs are mandatory to treat bacterial, parasitic or fungal infections, while the combination of antiviral agents and plasma exchanges has been proven to be effective against HBV-PAN. This latter strategy might also be effective against HIV-associated vasculitides and, unlike cytotoxic agents, does not jeopardize the outcome of HIV-infected patients. In the context of HCV-related cryoglobulinemic vasculitis, antiviral drugs are necessary to achieve recovery, in combination with low-dose corticosteroids and/or rituximab. In the near future, newer antiviral agents will probably also have their place in the therapeutic armamentarium for these patients.

**Introduction**

Infectious agents can be the underlying cause of several vasculitides, usually not associated with antineutrophil cytoplasmic antibodies (ANCA), and affect vessels of various calibers. There are two major virus-associated vasculitides (VAV); polyarteritis nodosa resulting from hepatitis B virus (HBV-PAN) infection (1), and cryoglobulinemic vasculitis (CV), occurring in patients infected with hepatitis C virus (HCV) (2). Other viruses can be associated, albeit less frequently, with the development of vasculitis (Table I): human immunodeficiency virus (HIV) (3), erythrovirus B19 (formerly parvovirus B19) (4), cytomegalovirus (CMV), varicella-zoster virus (VZV) and human T-cell lymphotropic virus-1 (HTLV-1). To treat these VAV, original therapeutic approaches have been devised that avoid prolonged administration of corticosteroids (CS) and cytotoxic agents. They are mainly based on the combination of antiviral agents and plasma exchanges (PE). Two prospective trials organized by the French Vasculitis Study Group (FVSG) validated that therapeutic strategy for HBV-PAN (5, 6). A specific antiviral strategy is also recommended for HCV-related CV, despite less favorable results (7, 8). On the other hand, syphilitic aortitis and/or cerebrovascular disease (9-11) and rickettsial diseases (12-14) often mimic primary systemic vasculitides. Other bacterial, fungal or parasitic infections may also be responsible for vasculitic features and are usually easier to diagnose because of their suggestive clinical manifestations such as 'mycotic aneurysm' in endocarditis or necrotizing and/or destructive lung vasculitis associated with Pseudomonas aeruginosa infection (15, 16). These latter vasculitides require specific antimicrobial therapy, with adjunctive CS only in very rare instances, but no immunosuppressant.

**Key words:** Systemic necrotizing vasculitides, secondary vasculitides, virus-associated vasculitis, HBV-related polyarteritis nodosa, cryoglobulinemic vasculitis, HCV-associated cryoglobulinemia, HIV infection.
I. Virus-associated polyarteritis nodosa

I. 1. HBV and other viruses associated with PAN: clinical presentation

Since the first reports on HBV-PAN (1, 17), this causal relationship has been largely confirmed based on clinical, epidemiological and therapeutic data (6). During the 1970s, about half of the patients with classic PAN were infected with HBV. However, over the past few years, the frequency of HBV-PAN has declined from 35% in 1984 to less than 5% today (18). In France, the HBV-PAN incidence has decreased dramatically since blood testing and donor selection were reinforced, and large vaccination campaigns were organized for teenagers and subjects at risk. Intravenous drug abuse has now become the predominant cause of HBV-PAN. Since 2002, fewer new cases of HBV-PAN but also PAN have been registered in France, which further, albeit indirectly, supports the hypothesis of a viral cause of PAN [HBV and/or other unidentified virus(es)].

Some other viruses have been also incriminated in PAN onset. HCV does not appear to be a major etiological factor for PAN and its responsibility has only rarely been advanced (19). Less than 5% of our PAN patients were infected with HCV (20). When present, HCV was often observed concomitantly with other viruses, HBV or HIV, and also with type II or III mixed cryoglobulinemia (MC). HIV infection has also been associated with PAN in several patients (3, 21-23), GB virus-C, when sought in patients with PAN, was occasionally found and could have been an underlying cause (24). Several concomitant erythrovirus B19 infections have been described but systematic testing of PAN patients did not show them to have a higher frequency of erythrovirus B19 infection than the general population (25, 26).

HBV-PAN usually becomes manifest less than 12 months after viral infection, with a mean of 4 months after exposure (6, 27), and occurs mainly in patients under 40 years old. Hepatitis is rarely diagnosed, as it is usually silent before PAN develops and remains absent or mild (2–3-fold transaminase-level rise) when PAN symptoms appear. Immune-complex deposition on and throughout vessel walls, in an excess amount of viral antigens, could trigger vasculitis and be responsible for subsequent organ damage. Clinical manifestations start suddenly and are roughly the same as those commonly observed in PAN (28). Orchitis, gastrointestinal and kidney vessel involvement, with hypertension, are common in HBV-PAN, whereas cutaneous and pulmonary symptoms are rarer (29).

HBV-PAN is certainly the purest form of PAN and no overlap with other vasculitides, especially microscopic polyangiitis, has been observed in our experience. Microaneurysms and/or stenoses may be seen on echomammographic and renal angiographies of medium-sized arteries in 40–62% of the patients without gastrointestinal symptoms, and in up to 90% with gastrointestinal involvement (30-33). HBe antigen (Ag) to anti-HBe antibody (Ab) seroconversion usually parallels recovery. The major sequelae are the consequence of vascular nephropathy and peripheral neuropathy but, even in patients who initially develop renal insufficiency, it is possible to cure PAN with little residual impairment of renal function.

I. 2. Outcome

Once remission has been obtained, HBV-PAN tends not to recur. In FVSG cohorts (28), only 6% of HBV-PAN patients relapsed, but it is still not possible to identify the subgroup of patients who will relapse. The clinical pattern of relapse does not necessarily mimic the original presentation, in that previously unaffected organs can be involved at relapse. Due to the low relapse rate, maintenance treatment is not necessary and short-term treatment can be envisaged.

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Table I. The main virus-associated vasculitides and their therapeutic management.

<table>
<thead>
<tr>
<th>Virus</th>
<th>Type of vasculitis</th>
<th>Standard therapy (see text for details)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>PAN</td>
<td>Short CS therapy, with PE and lamivudine</td>
</tr>
<tr>
<td>HCV</td>
<td>Cryoglobulinemic vasculitis</td>
<td>Short CS therapy, with IFNα and ribavirin ± PE (anti-CD20 ?)</td>
</tr>
<tr>
<td>HIV</td>
<td>PAN (controversial)</td>
<td>Short CS therapy, with ARV ± PE</td>
</tr>
<tr>
<td>Erythrovirus B19</td>
<td>PAN</td>
<td>CS</td>
</tr>
<tr>
<td>VZV</td>
<td>Retinitis</td>
<td>Acyclovir</td>
</tr>
<tr>
<td>CMV</td>
<td>Retinitis</td>
<td>Valganciclovir, ganciclovir or foscarnet</td>
</tr>
<tr>
<td>HLV-1</td>
<td>Necrotizing retinitis</td>
<td>Not established</td>
</tr>
</tbody>
</table>

ARV: antiretroviral drugs; CS: corticosteroids; IFNα: interferon-alpha; IVIg: intravenous immunoglobulins; PE: plasma exchanges.
I. 3. Deaths
The causes of death can be divided into three categories: related to vasculitis manifestations, attributed to treatment side effects and miscellaneous causes, usually independent of the vasculitis.

I. 3. 1. Vasculitis-related deaths
In all vasculitides, involvement of vital organs can be lethal. A few patients die early from multisystem involvement, often gastrointestinal (34), that cannot be controlled by treatment. In such cases, the course of the disease is generally characterized by fever, rapid weight loss, diffuse pain and involvement of one or several vital organs. Prognosis can also be evaluated using the French five-factor score (FFS), validated for PAN, microscopic polyangiitis and Churg-Strauss syndrome (Table II) (35). The FFS emphasizes the poor prognosis of specific gastrointestinal, renal, cardiac and/or central nervous system (CNS) involvement(s).

I. 3. 2. Deaths attributed to treatment side effects
Conventional treatment with CS and cyclophosphamide jeopardizes the patient’s outcome by allowing the virus to persist, stimulating its replication and thereby facilitating evolution towards chronic hepatitis and liver cirrhosis. Thus, cyclophosphamide, like prolonged CS administration, is contraindicated. In addition to these long-term side effects, infectious complications are more frequent when immunosuppressants are prescribed. PE can also favor the susceptibility to infections when central venous access is necessary, while CS are responsible for well-known side effects (34).

II. HCV-related cryoglobulinemic vasculitis
Type II and, more rarely, type III MC are the consequence of HCV infection in more than 80% of the patients (2, 36). MC can be detected in 30–50% of the patients infected with HCV but remains asymptomatic in most of them. CV is defined as a small-vessel vasculitis by the Chapel Hill Nomenclature (37). The disease duration, hepatic fibrosis or cirrhosis (19, 38, 39) might be factors associated with the presence of clinical symptoms in patients with MC (19, 40), whereas no clear association has been found between the HCV genotype and MC or CV (41–43). HLA DR11 (44), DR3 or DR4 (45) and B8 combined with DR3 (46) phenotypes were associated in some populations with an increased risk for the development of type II MC in patients with chronic HCV infection. Type II MC, usually with a monoclonal IgM-kappa component, is more frequent and characteristic of CV. Complement, especially the C4 component is low, and a rheumatoid factor may be found, and, because it is sometimes difficult to detect a cryoprecipitate, this biological context is highly suggestive of the diagnosis. AutoAb are absent, especially ANCA.

The more frequent symptoms of CV are purpura, painful leg ulcers, peripheral neuropathy, glomerulonephritis, arthritis and sicca syndrome (40, 47). The clinical symptoms (40, 47, 48) may develop progressively and are often of moderate intensity initially. Neuropathy can be symmetrical and limited to sensory signs, including hypoesthesia and pain, is usually distal, and occurs more frequently in the legs than arms. It can also take the form of mononeuritis multiplex, as described in PAN. The neuropathy tends to be chronic and, although the motor symptoms can regress, the sensory symptoms can remain definitively. Kidney involvement is glomerulonephritis but, unlike ANCA-associated vasculitides, pauci-immune glomerulonephritis is not found. Membranoproliferative glomerulonephritis is the hallmark of CV renal involvement, with some intracapillary thrombi containing cryoglobulin precipitates (49). Few patients progress to end-stage renal failure. About 20% of the patients have sicca syndrome but without the characteristic anti-SSA/Ro and/or SSB/La autoAb of Sjögren’s syndrome. Dilated and/or ischemic cardiomyopathy (47), ischemic cerebral stroke, cerebral vasculitis (50), ischemic intestinal perforations or hemorrhages (51) have also been described. The outcome of CV is characterized by chronicity and relapses, even under treatment.

III. HIV-associated vasculitis
Vasculitides occurring during the course of HIV infection have been reported (3, 23). According to Calabrese (23), the frequency is low (1%), with most of the reported cases having been identified at autopsy. In our experience (3), HIV-associated vasculitis is an extremely rare entity, which has been encountered in several large centers specializing in the management of HIV infection. This vasculitis can develop in adults and children at any HIV-infection stage, as defined by the Centers for Disease Control classification. Its clinical spectrum and histological findings vary widely. Most of them involved skin (often with digital ischemia or cry-
thrombocytopenia; Figure 1), peripheral neuropathy (mononeuritis multiplex (52)) or the CNS (ischemic stroke, focal neurological deficits or cerebral vasculitis). Cerebral lymphomas or granulomatous vasculitis have also been reported anecdotally (53). Large-, medium- and small-sized arteries can be affected. Necrotizing arteritis, non-necrotizing arteritis, giant-cell arteritis and eosinophilic arteritis have been observed (23).

Indeed, some cases seem to be caused by opportunistic infections, such as *Pneumocystis jiroveci* (formerly, *P. carinii*), CMV, VZV or *Toxoplasma gondii*, non-opportunistic infectious agents or drug-induced hypersensitivity. However, for most HIV patients who develop vasculitis, the exact cause remains unknown.

HIV was thought to be the etiological agent in a few patients because of the localization of the virus in the tissue lesions and the absence of evidence suggesting other mechanisms (52). The pathogenesis of these HIV-associated vasculitides is heterogeneous, but at least two general mechanisms have been hypothesized: virus replication might induce direct injury of the vessel wall or vascular damage might be the result of an immune mechanism. These mechanisms may be cellular and/or humoral and include deposition of immune complexes and/or their in situ formation (52). Indeed, immune complexes are frequently detected in HIV-infected patients and their frequency increases with advancing stages of infection (3). Some authors have analyzed their composition and found them to contain both HIV Ag and Ab specific to HIV. However, their role in the vasculitic process remains to be demonstrated.

### IV. Other virus-associated vasculitides

#### IV. 1. Erythrovirus B19

During the viremic phase of erythrovirus B19 infection, cutaneous leukocytoclastic vasculitis may develop, with purpuric lesions, with or without arthralgias, fever or abdominal cramps, mimicking Henoch–Schönlein purpura (54–56). Serological assays are helpful in distinguishing between the two diseases, when IgM directed against erythrovirus B19 are detected during the symptomatic acute phase. Some authors used polymerase-chain reaction (PCR) to detect erythrovirus B19 in endothelial cells and suggested a possible association with giant-cell arteritis (57), but this role remains controversial (58). Erythrovirus B19 infection, based on serology, has also been reported in some PAN (4), Kawasaki disease (59) and Wegener’s granulomatosis (60) patients, but these cases were most probably anecdotal.

#### IV. 2. Varicella-zoster virus

VZV vasculitis can develop in infected adults or children, during the acute primary infection, zoster recurrence or several weeks or months thereafter, and affects the CNS (61), retinal and/or choroidal small-vessels, and sometimes skin or kidney (62). Encephalitis and/or myelitis can be seen in immunocompromised patients, during acute infection, characterized by diffuse small-vessel vasculitis. CNS involvement may also occur several weeks after trigeminal zoster, and is manifested by a sudden ischemic cerebral stroke in middle cerebral artery-supplied areas. Cerebral angiography or magnetic resonance (MR) angiography may show ischemic lesions with artery irregularities and stenoses suggestive of medium- and small-sized vessel vasculitis (63). Viral PCR detection in leptomeningeal biopsies and cerebrospinal fluid is usual in this setting.

#### IV. 3. Cytomegalovirus

CMV-associated vasculitides can occur along with the virus direct pathogenic effects, mainly seen in immunocompromised patients, i.e. HIV-infected subjects or in bone-marrow recipients. Leading target organs are the gastrointestinal tract, mainly the large bowel, the CNS and skin (64). Characteristic cytological features of CMV infection in endothelial cells may be seen, arguing for a potentially direct vasculitis-inducing effect of the virus on small vessels (65). Possible gastrointestinal manifestations range from abdominal pain and febrile diarrhea to more severe bowel ischemia with perforations and/or hemorrhage (66). CNS involvement may be non-specific encephalopathy, cranial nerve palsies, meningitis, meningoencephalitis or radiculomyelitis. Vasculitis may be retained based on cerebral MR angiographic images, occasionally showing vessel irregularities or stenoses, or by histological examination, which is rarely feasible in practice (67, 68). Skin might be involved, especially when the viral infection is widely disseminated. Non-specific necrotic infiltrated purpuric lesions, subcutaneous nodules, vesicles or erythematous rash have been described (69). Finally, only rare cases of PAN or microscopic polyangiitis...
associated with CMV-infection serological markers have been reported.

IV. 4. HTLV-1

HTLV-1 is a human retrovirus highly endemic in the Caribbean islands, Africa, and southwestern Japan. It is almost always asymptomatic but may lead to adult T-cell leukemia/lymphoma (ATL) or myelopathy/tropical spastic paraparesis (TSP). Retinal vasculitis, with or without granulomatous and nécrotizing features in microdissected retinal biopsies, has been described in some patients carrying HTLV-1, in association or not with ATL, TSP or HTLV-1-associated uveitis, which is a more common ophthalmic manifestation of this viral infection (70, 71). HTLV-1-related cutaneous or CNS vasculitis is extremely rare (72).

V. Vasculitides secondary to bacterial, fungal or parasitic infections

Vasculitis onset following bacterial, fungal or parasitic infection results predominantly from direct invasion of endothelial cells, extension of a localized focus of infection involving blood vessels or septic haematogenous embolization. Blood cultures yield positive results and the germ can be identified in more than 50% of these episodes. Cutaneous biopsies, when skin is affected, may also contain microorganisms. Prompt antimicrobial therapy, combined with surgery when necessary, is mandatory in these cases. Autoimmune T- and/or B-cell reactions triggered by microbial antigens may play a role in some cases, perhaps because of epitope mimicry or superantigen induced T-cell activation. Antimicrobial therapy is also recommended, but regression of the lesions is more unpredictable. Putative infectious origins of primary systemic vasculitides, like, the potential responsibility in giant-cell arteritis of Chlamydia pneumoniae, whose DNA was detected in artery specimens from patients in 2001, but was subsequently questioned (58, 73, 74), are beyond the scope of this article.

Direct nécrotizing vessel-wall destruction can be induced by some bacteria, such as Pseudomonas aeruginosa or Legionella pneumophila in the lungs, or Fusobacterium necrophorum in the internal jugular veins after to pharyngitis. Mycobacterium tuberculosis, Mycobacterium spp., Aspergillus or Mucor (nécrotizing sinusal, orbital or intracranial vasculitis, with frequent arterial thromboses) (75), Coccidioides immitis (basilar granulomatous meningitis) (76), and Wuchereria spp. or Dirofilaria immitis (pulmonary vasculitis) (77) infections may also be involved in nécrotizing vasculitis, sometimes granulomatous and usually localized. Rarer cases of such localized vasculitides have been reported in patients infected with Histoplasma capsulatum (cerebral vasculitis), Cryptococcus neoformans (cerebral or skin vasculitis), Candida albicans (exceptional cases of cerebral vasculitis) or Malassezia furfur (pulmonary vasculitis) (78, 79), Toxocara, Schistosoma spp., Angylostrolyngus and Filariae infections have been associated with more diffuse forms of vasculitic diseases.

Septic embolizations result in the so-called ‘mycotic aneurysms’ (80–82), even though they do not usually lead to true aneurysm formation. These secondary vasculitic lesions are most frequently located in the aorta, followed by the intracranial, superior mesenteric or femoral arteries, and may be a consequence of infective endocarditis, especially when caused by Staphylococcus aureus or streptococc. However, they can also occur, albeit much more rarely, in some other settings, like infections with S. aureus, Streptococcus spp. or Salmonella spp. in intra-venous drug abusers, patients with osteomyelitis or in the elderly. Many other infective agents have been reported to cause mycotic aneurysms, at diverse arterial locations, including Clostridium septicum (83), Burkholde ria pseudomallei (84), Aspergillus (85) or after intravascular BCG therapy for bladder cancer (86, 87). Smaller vessels may also be affected, with peripheral septic embolizations, particularly in the skin, resulting, e.g., in erythema gangrenosum, which is usually associated with Pseudomonas aeruginosa or Gram-negative bacteremia in neupropenic patients, and is a 1- to 5-cm macular indurated lesion with a central nécrotic ulceration. Disseminated infections with Nocardia, Aspergillus or Mucor spp. may result in erythema-like lesions, mostly in immunocompromised patients. Neisseria meningitides bacteremia is often associated with a diffuse macular and purpuric rash, with evidence of nécrotic vasculitis and presence of the germ in endothelial cells and surrounding mononuclear cells in skin biopsies, when taken.

Syphilitic aortitis and cerebrovascular disease have become rare since the advent of penicillin, which still constitutes their reference treatment, but have not disappeared, primarily due to the HIV epidemic. These lesions are classic vascular lesions of tertiary syphilis, and usually develop, respectively, 10–30 and 6–10 years after the first stage of the infection. TPHA testing of sera and cerebrospinal fluid from these patients for Treponema pallidum is usually positive. The non-treponemal VDRL test is often negative for serum, but can be positive for cerebrospinal fluid from 30–70% of the patients with cerebrovascular syphilis and has high specificity in these cases. Conversely, TPHA-positive cerebrospinal fluid is not diagnostic of neurosyphilis, because it has been seen in patients with no signs, but it has a strong negative-predictive value, ruling out the diagnosis when negative (88). T. pallidum is only rarely detected in artery wall lesions.

The microorganisms responsible for rickettsial diseases are obligate intracellular bacteria that can cause vasculitis, especially with skin manifestations (maculopapular extensive rash) in Rocky Mountain spotted fever, which can, if it goes unrecognized and untreated, involve kidney (renal impairment), lung (pulmonary edema) or even brain small vessels in up to 25% of the patients, but also in boutonneuse fever or epidemic typhus. The diagnosis is mainly based upon clinical findings, since serological testing can confirm it only later, whereas antibiotics are indicated as soon as possible. Borrelia burgdorferi has infrequently been reported to cause CNS vasculitis (89).
Erythema nodosum leprosum is characterized by painful cutaneous nodules, evolving towards ulcerations, that develop in half of the patients with lepromatous leprosy after the initiation of antimicrobial therapy and are often associated with general symptoms, neuropathy, uveitis and occasionally with glomerulonephritis. Biopsy of skin lesions can reveal features of acute small-vessel vasculitis, thought to be due to immune-complex vascular deposits and/or excessive local T-helper type 1 (Th-1) lymphocyte activation, triggered by the release of mycobacterial debris after starting antibiotic treatment. Adjuvant and short-term CS may be necessary in some of these patients and is usually effective.

**VI. Treatment**

Treatment objectives are two-pronged, to simultaneously treat the infection and the associated vasculitis, with drugs and therapies that do not interfere each other. Indeed, treatment for vasculitides caused by bacteria, fungi or parasites primarily relies on antimicrobial agents alone, and only rarely require CS. For VAV, strategies have now been well defined, using CS and/or immunosuppressants principally for patients in whom antiviral drugs and/or PE have not achieved recovery or as an initial adjuvant therapy for the most severe forms (Table I).

**VI.1. Treatment of HBV-PAN**

For many years, HBV-PAN was treated in the same way as non-virus-related PAN, with CS being prescribed sometimes in combination with cytotoxic agents, mainly cyclophosphamide. This regimen was often effective in the short-term but careful analysis of long-term results showed that relapses and complications (chronic hepatitis or liver cirrhosis) occurred because of virus persistence. According to McMahon et al. (90), who followed Eskimos with PAN, four (31%) patients died during the course of PAN. In our first randomized study (91) in which PAN patients were not selected according to their viral status, 14/71 were HBV-positive; 84% of them recovered from PAN but two subsequently died of liver cirrhosis.

The rationale for combining PE and antiviral drug(s) was to obtain the following effects: initial CS to rapidly control the most severe life-threatening manifestations of PAN which are common during the first weeks of the disease, and abrupt stoppage of CS to enhance immunological clearance of HBV-infected hepatocytes and favor HBeAg to HBeAb seroconversion. PE can almost always control the course of these PAN without the addition of steroids or cyclophosphamide. An alternative therapy was also needed to lower HBV-PAN mortality and improve prognosis. In a retrospective study, we showed that, when CS and immunosuppressants were prescribed to treat HBV-PAN, the outcome was poorer than for non-viral-PAN (28). Therefore, based on the efficacies of antiviral agents against chronic hepatitis and of PE in PAN, together with Trépo and Thivolet’s description of HBV responsibility in the development of PAN (1), we combined the two therapies to treat HBV-PAN (92, 93). However, in our protocol, CS are still prescribed for 1 week to help control as quickly as possible the clinical manifestations while waiting for the antiviral agent’s efficacy to kick in.

**VI.1.1. Vidarabine**

When this therapeutic strategy was first applied, vidarabine was the only available antiviral drug. After a 3-week course of intravenous vidarabine (15 mg/kg/d for 1 week then 7.5 mg/kg/d for 2 weeks), administered after 1 week of CS (prednisone, 1 mg/kg/d) and combined with PE, a full clinical recovery was obtained in three-quarters of the patients and HBsAg seroconversion was observed in nearly half of the patients. However, vidarabine’s high neurological and hematological toxicities finally lead to its replacement by less toxic agents, like IFNα and lamivudine.

**VI.1.2. Interferon-alpha**

Furthermore, IFNα gave better results than vidarabine. In a series of patients, HBe seroconversion was obtained in two-thirds of the patients and HBsAg–HBsAb seroconversion in half of them. The dose of 3 million units, injected subcutaneously 3 times a week is recommended. In the case of failure, the dose could theoretically be increased to 6 millions units, injected subcutaneously, 3 times a week. Pegylated IFNα, validated for the treatment of hepatitis C, could probably also be prescribed for HBV-PAN, in analogy with what is being done in ongoing trials on chronic hepatitis B (94).

In HBV-PAN, the combination of antiviral agents (vidarabine or IFNα-2a or -2b) gave excellent overall therapeutic results (6). The efficacy of this strategy was confirmed in a series of 41 patients (6); 23 (56%) no longer exhibited serological evidence of replication and 81% have completely recovered.

**VI.1.3. Lamivudine**

Lamivudine is an antiviral agent specifically designed for the treatment of HBV and HIV infections. In a first cohort of 10 HBV-PAN patients (5), we prescribed lamivudine (100 mg/d) in combination with PE, after a few days of CS. Because lamivudine is eliminated by the kidney, its dose should be adapted to renal function and lowered for patients with renal insufficiency. In that study, 9/10 patients recovered (1 died from catheter-related septicemia) and 6/9 HBe seroconverted. We concluded that, because of its oral administration and good safety profile, lamivudine should henceforth, and to date, be considered the antiviral agent of choice to treat HBV-related PAN. For patients who do not seroconvert after a well-conducted 6-month course of therapy with lamivudine alone, newer antiviral agents or a combination of several of them or lamivudine and IFNα should probably be proposed.

**VI.1.4. Newer antiviral drugs, potentially useful in treating HBV-PAN**

Adefovir dipivoxil is a more recent antiviral drug that has been shown to be as effective and as well-tolerated as lamivudine in the treatment of chronic hepatitis B. Furthermore, oral adefovir dipivoxil (10 mg/d) also led to histological improvement in 53% of the patients with chronic hepatitis B (95,
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96), and can be effective against lamivudine-resistant virus strains (96), alone or in combination with other newer molecules (entecavir, emtricitabine, clevudine) (97-99). These drugs could probably be effective against HBV-PAN, but trials will be difficult to set up, because of the decreasing incidence of HBV-PAN over the past few decades.

VI.1.5. Plasma exchanges

An antiviral agent was prescribed alone to a few patients (100). In our opinion, even if it is sometimes possible to obtain good clinical results, the severity of the vasculitis in most patients requires therapy able to control immediately the severe or potentially life-threatening manifestations of PAN. Because PE are able to rapidly clear the immune complexes responsible for the disease, they are the most appropriate means to control the disease. In our opinion, PE are not indicated because of their superiority over other medications but because they are, in combination with antiviral drugs, able to replace the harmful therapies commonly used to treat VAV with equivalent efficacy.

The optimal schedule is as follows: 4 sessions/week for 3 weeks, then 3 sessions/week for 2–3 weeks, followed by progressive lengthening of the intervals between sessions. One plasma volume (60 ml/kg) is usually exchanged using 4% albumin as the replacement fluid. The circuit can be primed with starch. During the first weeks of treatment, the high number of PE can decrease the level of clotting factors and thereby facilitate bleeding. Should bleeding occur, fresh-frozen plasma can be used instead of albumin. Tolerance of PE is usually excellent.

VI.1.6. Outcome and follow-up

The previously described short- and long-term outcomes of the patients showed the progressive improvement of seroconversion rates for patients receiving antiviral therapy. One of the major advances obtained under our antiviral strategy was the very rapid cure of HBV-PAN, even in its most severe forms. The majority of patients received the antiviral drug for a few weeks or months while PE, which were specifically given to control the acute manifestations of the disease, were stopped after 2 months. Signs of vasculitis were sometimes eliminated more quickly, with some of our patients recovering within 3 weeks.

In the days following treatment onset, transaminase levels increased but they usually returned to normal within a few days or weeks. For patients given vidarabine, a second increase of transaminase levels was observed prior to seroconversion. This usually mild immunological response was considered normal, as it attested the ability of the patients’ hepatocytes to clear the virus. Nevertheless, transaminase levels can rise sharply and fulminant hepatitis can coincide with HBe seroconversion, as for one of our patients (101), who died of fulminant hepatitis several days after seroconversion. The response observed under IFNα or lamivudine is markedly different: transaminases normalize progressively and their levels do not rise after stopping the treatment, even when seroconversion has not been obtained. When HBeAg are detected, PE should be stopped to avoid the clearance of the newly synthesized immunoglobulins. Several patients’ Ab levels fluctuated, sometimes being present or absent. This Ag-Ab equilibrium can be very unstable and treatment should then be continued. In such cases, it is more reliable to monitor virus activity by quantitative measurements of viral DNA.

After the patient’s recovery from the symptoms of the vasculitis, the clinician potentially faces two different virological situations. First, replication continues, as demonstrated by the absence of HBeAb and the positivity of viral DNA, and PAN remission has been obtained but relapses may still occur. In this situation, we recommend focusing on the treatment of viral hepatitis and not PAN, which has been cured, using an adapted and up-to-date antiviral strategy. Second, Ab to HBe, at least, or to HBs, at best, are present, the patient can be considered cured and relapses will, for the majority of the cases, probably never occur. If, despite the presence of anti-HBsAb, new manifestations of PAN appear, the clinician should consider the possibility of the vasculitis occurring coincidentally with virus infection but not linked to it.

VI.2. Treatment of HCV-associated cryoglobulinemic vasculitis

Treatment of chronic hepatitis C and CV must be clearly distinguished. First, for asymptomatic patients, there is no argument to treat, and monitoring could be sufficient. For symptomatic patients, it should be underlined that no treatment is able to cure the majority of them definitively and that an optimal therapeutic strategy has not yet been clearly defined.

VI.2.1. Medicamentous therapies

According to one study (102), only a quarter of the patients with chronic hepatitis C achieved a sustained virological response under treatment, whereas other authors (103) reported that 69% of their patients had responded to pegylated IFNα at 48 weeks and achieved clinical recovery. Combining IFNα and ribavirin may increase the seroconversion rate, with a sustained response rate for treatment-naive patients of about 55% (104).

CS and immunosuppressants are commonly used to treat severe symptomatic forms, but they have the same noxious effects as discussed above for HBV-PAN. As for HBV-PAN, we devised a strategy (105) combining antiviral drugs and PE. For patients with moderate symptoms of CV (e.g., arthralgias, purpura, sensory peripheral neuropathy), combining IFNα and ribavirin is indicated. Ribavirin alone is not able to completely suppress viral replication but, in conjunction with IFNα, viral replication was no longer detectable in 48% of the patients who had received the combined regimen for 12 months (102). We can expect that virus suppression will also be obtained in cryoglobulinemia. It is worth noting that IVIg have been proven ineffective against peripheral neuropathy in this setting (106). More recently, therapy with pegylated IFNα-2b and ribavirin (for a mean of 13.5 months) was effective in an open study (107) on 9 patients with CV. 7 of them mounted clinical and virological responses, sus-
tained for 18.6 months after the end of therapy, and serum MC disappeared in 5 of them.

Although the majority of the patients seen for symptomatic MC have virus-positive PCR assays, reflecting virus replication, a few of them remain serologically positive but become PCR-negative, reflecting past contamination. We also observed, in two of our patients with very severe CV, the disappearance of the virus under combined antiviral therapy and PE but the persistence of clinical symptoms, which necessitated prolonged symptomatic treatment with PE.

VI.2.2. Plasma exchanges

The indications of PE in HCV-related MC and CV are controversial. Based on their effectiveness documented in our patients who failed to respond to other treatments, we recommend combining PE and antiviral drugs (5, 110). PE should not be prescribed systematically for every newly diagnosed case of MC because the majority of patients present no or very few symptoms, and we still do not know whether or not treatment is indeed indicated in these paucitoxic or asymptomatic forms.

PE are indicated for patients with symptoms requiring therapeutic intervention. Purpura and sicca syndrome do not constitute such indications: the former regresses spontaneously and the latter is refractory to them. In the case of glomerulonephritis due to CV, PE combined with pegylated IFNα and ribavirin can be effective but randomized controlled trials are needed to assess their contribution. PE are mainly indicated to treat rapidly progressing peripheral neuropathy and chronic leg ulcers. The latter manifestation is often very severe and accompanied with pain that can require intensive therapy, including morphine. Under PE, anteropodeal ulcers regress quickly and complete healing can be obtained in a few weeks. PE should be tapered progressively to avoid a rebound phenomenon due to the increased synthesis of cryoglobulins as a consequence of the stimulation of the B-cell clones responsible for their production. Some of our patients remain PE-dependent; clinical symptoms recur or worsen during tapering or after abrupt discontinuation of the sessions. Maintenance treatment should therefore be prescribed and the clinician has to try to determine the minimal number of sessions able to control the disease.

When indicated, the number of sessions is not clearly established. We recommend the following schedule: 3 sessions/week for 3 weeks, then 2 sessions/week for 2-3 weeks, then 1 session every week or every 10 days until clinical symptoms disappear or the optimal clinical result is obtained.

VI.3. Treatment of HIV-associated vasculitides

Treatment of HIV-associated vasculitides has not yet been well defined, and CS and immunosuppressants should be used cautiously, as they could favor the development of opportunistic infections and other clinical manifestations of HIV infection. Again, the dual objective is to cure the vasculitis and to control HIV infection, and thus to avoid CS and cytotoxic agents.

The first objective is HIV-replication suppression, which is more easily obtained with a combination of antiviral agents. Based on the presence of immune complexes, we have proposed, as for other VAV, to treat the patients with PE, using the same schedule as that for HBV-PAN. PE can clear immune complexes and cytokines involved in the vasculitic process. In our clinical experience, this regimen was successful (3), since the patients we treated improved and recovered from vasculitis. This strategy was also effective for patients with HIV and HCV or HBV confections. Some patients with CV responded very quickly to this therapy, CV symptoms usually recur after stopping PE and, unfortunately, anti-HIV drugs are not able to suppress cryoglobulin production. We also detected anti-cardiolipin Ab in a patient with HIV- and HCV-related vasculitides. HIV-associated vasculitides appear to be a one-shot disease and do not recur. 1-3 months of therapy are usually sufficient to cure them.

VI.4. Treatment of the other virus-associated vasculitides

Spontaneous recovery in a few weeks is the general rule for cytomegalovirus B19-related cutaneous vasculitides. However, severe or systemic symptoms may warrant CS for several weeks or months. IVIg have also been used successfully in some cases (111).

Vasculitides caused by VZV or CMV are often severe and life-threatening. Intravenous acyclovir has to be prescribed for VZV-CNS vasculitides, even though the diagnosis is often obtained too late for therapy to be effective. Prompt antiviral therapy, with oral valganciclovir for the milder manifestations (retinitis) but mostly intravenous ganciclovir and/or foscarnet, is mandatory for CMV vasculitides. CS clearly must be avoided in these patients, who are usually severely immunocompromised.

VI.5. Treatment of vasculitides caused by bacteria, fungi or parasites

In the case of vasculitis resulting from extension of a localized infection or septicemia, antimicrobial therapy directed against the specific pathogen is mandatory and will not be extensively detailed here, with prompt surgical intervention when needed, e.g., in case of large bacterial abscesses, destructive endocarditis or true mycotic aneurysms that increase in size or fail to resolve despite adapted medical therapy. However, no guidelines for the indication and timing of surgery in these latter conditions have been published to date.

The effect of antibiotics on syphilitic aortitis and cerebrovascular syphilis is unclear, but they may accelerate recovery and/or limit vascular scar formation and damage. Recommended regimen consist of 3 doses of 2.4 MU of benzathine penicillin at weekly intervals for syphilitic aortitis, and IV aqueous crys-
Itallic penicillin G 3-4 MU every 4 h for 10-14 days for neurosyphilis, or IM procaine penicillin 2-4 MU once daily in combination with probenecid 500 mg orally 4 times a day, both for 10-14 days, if compliance can be ensured (112). Rickettsial diseases are mainly treated with doxycycline 100 mg orally twice daily for 7-10 days, or until the patient becomes afebrile, with ciprofloxacin being an alternative for bouloneuse fever.

**Conclusion**

Vasculitides occurring secondary to infections with microorganisms are not uncommon. A potential microbial cause must be sought because it requires a specific therapeutic approach. Adapted antimicrobial agents should be prescribed to treat vasculitides of bacterial, fungal or parasitic origin. The combination of antiviral agent(s) and antibiotics may be prescribed to treat vasculitides of viral origin. A specific therapeutic approach is required in cases of vasculitis secondary to infections with microorganisms, or in cases of vasculitis associated with viral infections (in French). Presse Med 2004; 33: 1731-81.

**References**

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