Bartonella and Coxiella infections presenting as systemic vasculitis: case series and review of literature

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Key messages:

- **Bartonella infections in the context of endocarditis can mimic ANCA-associated vasculitis**
- **Coxiella infections can mimic vasculitis of all vessel sizes, through cryoglobulinemia or direct vascular infection**
- **Knowing these features can avoid wrongfully treating patients exclusively with immunosuppressors instead of antibiotics**

Abstract

Background. *Coxiella* and *Bartonella sp.* display particular tropism for endothelial or endocardial tissues and an abnormal host response to infections with induced autoimmunity. However, no study describes the characteristics of vasculitis caused by these agents.

Methods. We retrospectively included cases of definite *Coxiella* and *Bartonella* infections presenting with vasculitis features and performed a comprehensive literature review.

Results. Six cases of *Bartonella* infections were added to 18 cases from literature review. Causative pathogens were mainly *B. henselae*. *Bartonella* infection mimicked anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis in 83% with PR3-ANCA and presented as cryoglobulinemic vasculitis in 8%. Glomerulonephritis was present in 92%, and 88% had endocarditis. Complement fractions were low in 82% and rheumatoid factor positive in 85%. Kidney biopsies showed cell proliferation, mostly crescentic, with pauci-immune glomerulonephritis in 29%. Outcome was favorable, with the use of antibiotics alone in one third. Five cases of *Coxiella* infections were added to 16 from literature review. Sixteen had small-vessel vasculitides, mainly cryoglobulinemia vasculitis in 75%. One patient had polyarteritis nodosa-like vasculitis and four large-vessel vasculitis. Endocarditis was present in 69% of patients with small-vessel vasculitis but in none with medium or large-vessel vasculitis. Outcome was good except for one death. A highly sensitive next generation sequencing analysis on 3 *Coxiella* and 2 *Bartonella*-related vasculitides biopsies did not find any bacterial DNA.

Conclusion. *Coxiella* and *Bartonella* are both able to induce vasculitis but display distinct vasculitis features. *Bartonella* mimics PR3-ANCA-associated vasculitis in the setting of endocarditis, whereas *Coxiella* may induce vasculitis involving all vessel sizes.

Introduction

According to the 2012 International Chapel Hill Consensus Conference, vasculitides are dichotomized into primary vasculitides and secondary vasculitides with probable etiology. In the latter, etiologies mostly include drugs and infections such as hepatitis B virus-associated polyarteritis nodosa (PAN), hepatitis C virus-associated cryoglobulinemia vasculitis (CryoVas) and syphilis-associated aortitis[1]. Distinguishing primary from secondary vasculitides is of outmost importance as timely diagnosis is necessary for appropriate care. *Coxiella burnetti,* the causative agent of Q fever, is known for its ability to infect endothelial cells especially endocardium, native vascular tissue or even prosthetic grafts. In addition to its infectious potency, observations suggest a unique ability to induce autoimmunity[3]. *Bartonella henselae* and *Bartonella quintana* also display a particular tropism for endocardial tissue and are responsible for 1 to 4% of endocarditis, depending on geographical area[4]. Recently, it has been reported that antineutrophil cytoplasmic antibodies (ANCA) were frequently positive in *Bartonella* endocarditis[5].

Given the vascular tropism of these bacteria and their ability to induce autoimmunity, rare cases of secondary vasculitides caused by *Coxiella* and *Bartonella* infections that may sometimes present as primary vasculitides, have previously been reported. There is to date no comprehensive review describing vasculitides associated with these infectious agents. In this present study, we combine a significant case series and a comprehensive literature review of *Coxiella* and *Bartonella* infections to outline their clinical, biological and histologic presentation, as well as their outcome.

Methods

Patients

We performed a retrospective study based on a national survey to identify patients with vasculitis manifestations revealing *Coxiella* or *Bartonella* infections, supported by the French Vasculitis Study Group (FVSG), a nationwide research collaboration group in the field of systemic vasculitis.

Patients were included if they had clinical manifestations of vasculitis (purpura, arthralgia, myalgia, kidney involvement, peripheral neuropathy), in association with suggestive immunological (ANCA and cryoglobulinemia positivity), radiological [computed tomography (CT), positron emission tomography (PET)-CT, magnetic resonance imaging (MRI), and/or angiography] and/or histological features (leukocytoclastic, granulomatous or necrotizing vasculitis, crescentic glomerulonephritis), together with a proven infection by *Coxiella burnetti* or *Bartonella sp*. A proven infection was defined as a positive bacteriological test [serology, PCR (polymerase chain reaction), and/or culture] with organ specific damage and/or ineffectiveness of immunosuppressors alone.

Next-generation sequencing (NGS)

To determine if in-situ tissue infection was responsible for organ damage, available tissue was tested with a shotgun metagenomic procedure, an unbiased and highly sensitive accredited method (ISO15189) to detect any microbial DNA[6]. Briefly, tissues were extracted using a pretreatment combining bead beating, chemical and enzymatic lysis with extraction by DNA Blood kit on QiaSymphony instrument (Qiagen). DNA and RNA were prepared for sequencing by means of Nextera XT and TruSeq Stranded Total RNA library kits (Illumina) respectively and sequenced with NextSeq 500/550 High Output Kit v2.5 (300 Cycles) (Illumina) on NextSeq500 (Illumina). Analysis was performed with MetaMIC software in order to document and quantify microorganisms. All runs included environmental (sterile water) and positive control Microbial community Standard (ZymoBiomics).

Literature Review

We performed a comprehensive literature search of cases with *Coxiella* or *Bartonella* infection and clinical manifestations of vasculitis. We searched Medline via PubMed for all articles in English, French or Spanish using the key words or mesh terms “coxiella”, “bartonella”, “q fever”, “vasculitis”, “purpura”, “ANCA”, “cryoglobulinemia”, “giant cell arteritis”, “Takayasu”,

"polyangiitis", "polyarteritis nodosa" and "leukocytoclastic vasculitis". Only reports with clinical, biological, bacterial and histologic data when performed were included.

Statistics

Descriptive statistics included mean (standard deviation) or median (interquartile range) for continuous variables and frequency (percentage) for categorical variables.

Competing interest

Authors declare no competing interest in the realization of this work.

Ethics

The collection of data was retrospective and observational. Data collection and analyses were approved by the Ethic Review Committee of Cochin University Hospital (decision number AAA-2021-08020). The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Bartonella infections

We included six original cases of *Bartonella* infection and 18 patients from the literature review[7–24]. All cases are detailed in **Table 1**. Most patients were men (16/24, 67%), median age was 62.5 (IQR 46.5-69) years and 13 (54%) had a pre-existing valvulopathy or prosthetic valve. Median delay between symptoms onset and diagnosis was 2.8 months (1.6-5). Twenty-one (88%) patients had negative blood culture for common infectious endocarditis, with pathogen documented by serology in most cases (79%) with IgG positive in 92% and IgM in 80%, or PCR, performed on excised tissue (38%) or blood samples (17%). Causative pathogens were *B. henselae* in 16 (67%) patients, *B. quintana* in 7 (29%) and *B. bacilliformis* in one case.

Bartonella infection mimicked ANCA-associated vasculitis (AAV) in 20 (83%) cases and presented as cryoglobulinemic vasculitis in 2 (8%) and leukocytoclastic vasculitis in 1 (4%). The last patient,

with an underlying IgA vasculitis, presented a new vasculitis flare concomitant with *Bartonella* infection. Main symptoms were fever (59%), purpura (41%) and arthralgia (23%). Kidney involvement was present in 22 (92%) cases, proteinuria and hematuria respectively in 20 (83%). Median serum creatinine at presentation was 206µmol/L (IQR 186-308). Among ANCA-positive patients, proteinase 3 (PR3) was the most frequent specificity (80%). Unusual for AAV, complement fraction levels were low in 14/17 (82%) of cases and rheumatoid factor was positive in 11/13 (85%). The most common finding in kidney biopsies was cellular proliferation in 18/20 (90%) cases, with crescents in 14/18 (78%) but also endocapillary proliferation in 4/18 (22%), membranous proliferation and mesangial proliferation in 2/18 (11%) patients, respectively. Immunofluorescence analysis on renal lesions showed glomerular immune deposits in 12/17 (71%). Only 5 (29%) patients displayed typical pauci-immune crescentic glomerulonephritis, all having positive ANCA and low complement levels.

All patients received antibiotics, in association with glucocorticoids in 13/24 (54%), and cyclophosphamide in 7/24 (29%). Therapeutic plasma exchanges were performed in 3/24 (13%) cases, and 10 (42%) patients required valvular replacement. Strikingly, all cases treated with immunosuppressors alone without proper antibiotic regimen deteriorated or relapsed.

No death from infectious cause or vasculitis was reported. Renal outcome was good with a median serum creatinine of 108µmol/L (IQR 96.5-122.5) at last follow-up.

Coxiella Infections

We included five new cases of *Coxiella* infection and 16 patients from the literature review. Detailed case descriptions are reported in Table **2**. Most patients were male (14/21, 67%), and median age was 61 (IQR 54.5-65.5) years. Animal exposure or rural habitat was documented in 8/21 (38%) cases. All patients had positive Coxiella serology, 2 had positive PCR in the blood and

6 positive within tissues. Eleven (52%) patients had definite infectious endocarditis. Median delay between symptoms onset and diagnosis was 5.5 months (2.5-6.5).

Sixteen (71%) patients had small-vessel vasculitis presenting as purpura (n=10), glomerulonephritis (n=7), livedo (n=1), arthralgia (n=1) and/or peripheral neuropathy (n=1). Mixed cryoglobulinemia was detected in 12/16 (75%) patients, and PR3-ANCA was positive in 2/16 (13%) cases. Two patients with negative immunological workup had perivascular neutrophilic infiltrate with fibrinoid changes on skin biopsy, consistent with leukocytoclastic vasculitis without any aspect of thrombotic vasculopathy.

One patient had medium-vessel vasculitis presenting as polyarteritis nodosa (PAN) with fever, myalgia and hepatic artery aneurysm. Finally, 4 patients had large-vessel vasculitis mimicking either giant cell arteritis (GCA) (n=3) or Takayasu arteritis (n=1). One patient had temporal artery biopsy showing features suggestive of giant cell arteritis, and one patient had giant cells on histological analysis of the aorta with a positive *Coxiella* PCR on tissue. None of these five patients had endocarditis.

All patients received antibiotics, including tetracyclines in 100% associated with hydroxychloroquine in 86% of cases. Eight patients also received immunosuppressive agents, 4 with cryoglobulinemic vasculitis, 3 with large-vessel vasculitis and 1 with PR3-ANCA vasculitis. Only one patient with cryoglobulinemic vasculitis and positive blood *Coxiella* PCR was successfully treated with rituximab after inefficiency of antibiotics and glucocorticoids. Outcome was favorable in all but one patient.

Tissue NGS Results

Four skin biopsies of purpuric lesions and one kidney biopsy were tested using NGS, including 3 from *Coxiella*-infected patients and 2 from *Bartonella* infections. No microbial DNA was detected

in any of these five samples despite a good depth of sequencing above recommendations for this test (>20 million sequences per samples)[25].

Discussion

We describe here characteristics of *Bartonella* and *Coxiella* infections presenting as systemic vasculitis through an original case series and a comprehensive literature review. This study provides original insights into the presentation, treatment and prognosis of infection-associated vasculitis.

Bartonella infections most commonly induced small-vessel vasculitis with clinical features mimicking renal-limited PR3-ANCA vasculitis in the setting of endocarditis. Endocarditis from any origin has been shown to induce ANCA positivity in 19 to 24% of cases[26], whereas this prevalence can be as high as 60% in *Bartonella* endocarditis[5]. In our study, ANCA positivity was more frequently associated with *Bartonella* than *Coxiella* infections as was glomerulonephritis. Expression of complementary epitopes at the surface of *Bartonella spp.*, could induce a molecular mimicry phenomenon leading to the production of pathogenic autoantibodies, as it was discovered for anti-LAMP-2 antibodies induced by gram-negative bacteria[27].

Whether ANCA induce vascular damage in endocarditis is up to debate. Although MPO-ANCA can induce vasculitis in murine models[28], a direct pathogenic role of PR3-ANCA was not clearly demonstrated so far[29]. Although a retrospective study has suggested that kidney involvement tends to be more frequent in ANCA-positive endocarditis[26], our study does not support a pathogenic role of ANCA. Immunofluorescence analysis in kidney biopsies showed immune deposits in the vast majority of cases in association with hypocomplementemia, suggesting the role of immune complexes in organ damage. Moreover, renal outcome was usually favorable in our study despite limited use of immunosuppressors, supporting a non-pathogenic role for ANCA.

Three major red flags should alert physicians towards an infectious origin when considering glomerulonephritis with ANCA positivity. First, was the absence of ENT involvement and a single occurrence of pulmonary nodules in a context of tricuspid endocarditis in our series, whereas it is prevalent in up to 73% and 45% respectively of patients with granulomatosis with polyangiitis (GPA)[30]. Second, low complement fraction levels were observed in the majority of cases, even in pauci-immune crescentic glomerulonephritis, which is highly unusual in GPA. Deshayes *et. al* reported hypocomplementemia in 5% of AAV[31]. This finding is similar to data from the FVSG database, showing low C3 and C4 levels in only 1.3% and 3.9%, respectively (unpublished data). Third, in case of glomerulonephritis, renal biopsy seems essential to reconsider AAV diagnosis in case of complement and immunoglobulin deposition. Physicians should therefore suspect an underlying *Bartonella* infection in case of PR3-ANCA glomerulonephritis with low complement fractions levels, lack of ENT involvement and positive immunofluorescence on kidney biopsy.

Mixed cryoglobulinemia was another frequent cause of small-vessel vasculitis in our study, especially during *Coxiella* endocarditis. *Coxiella* is able to induce multiple forms of autoimmunity through autoantibody formation[2]. It seems therefore plausible that, in predisposed subjects, the immune response to *Coxiella* infection could transiently trigger formation of autoantibodies. To support this hypothesis, our study did not find any trace of in-situ tissue infection on 3 small vessel vasculitis biopsies, suggesting immune-mediated organ damage. Only one case from the literature showed an unfavorable outcome with antibiotics alone and required rituximab infusions. Remaining cases had a favorable outcome with antibiotic treatment alone, as expected in infectious cryoglobulinemia[32]. These cases show the need for a thorough workup to eliminate an infectious origin in case of cryoglobulinemic vasculitis.

Medium and large-vessel vasculitides were observed only in the setting of *Coxiella* infections and without associated endocarditis. Specific PCR was positive on aortic tissue in one patient. Julia et. al described the presence of necrotizing granulomas in more than half of patients

with Q fever aortic aneurysms, with the presence of giant cells in two specimens[33]. We therefore suggest that in contrast with small-vessel vasculitis, it rather is in-situ microbial infection of medium or large-vessel which results in a granulomatous immune response mimicking granulomatous vasculitis such as GCA or Takayasu arteritis.

Overall, our study shows distinct vasculitis patterns between *Bartonella and Coxiella* infections. *Bartonella* infections mainly mimic primary small-vessel PR3-ANCA vasculitis with predominant or exclusive kidney involvement, whereas *Coxiella* infections can induce both small vessel mixed cryoglobulinemia vasculitis, medium vessel vasculitis and granulomatous large vessel vasculitis.

Table 1 : Case description of vasculitides caused by Bartonella infections

Age	Sex	Case origin	Mimicked Vasculitis	Endocarditis	Clinical findings	Microbiological diagnosis	Immunology workup	Pathological findings	Antibiotic treatment	Immuno-suppressors	Outcome
67	M	Our series	AAV	Yes	Pulmonary oedema, AKI, hematuria, proteinuria	B. Quintana serology	Anti-PR3, low C3/C4	Membranous proliferative GN with immune complexes	Doxycycline, Amoxicillin, Gentamicin	-	Good
87	F	Our series	AAV	Yes	Fever, necrotic purpura, pulmonary oedema, heart murmur, AKI, hematuria, proteinuria	B. Henselae serology	Anti-PR3, low C3, RF	Skin leukocytoclastic vasculitis with immune complexes	Doxycycline, Amoxicillin, Gentamicin	-	Good
78	M	Our series	AAV/CryoVas	Yes	AKI, proteinuria, hematuria	B. Henselae blood + aortic valve/blood PCR	Anti-PR3, cryoglobulinemia, low C3, RF	Pauci-immune crescentic GN	Doxycyclinee, Rifampicin	GC, CYC, Plasmatic exchanges	LFU
48	F	Our series	AAV	Yes	Purpura, pulmonary nodule, proteinuria	B. Henselae serology + blood PCR	Anti-PR3, RF	Crescentic GN with immune complexes	Doxycycline, Gentamicin	-	LFU
54	M	Our series	AAV	Yes	AKI, proteinuria, hematuria	B. Henselae serology + aortic valve PCR	Anti-PR3, cryoglobulinemia, low C4, RF	Pauci-immune crescentic GN	Amoxicillin, Vibramycin, Gentamicin	GC, Plasmatic exchanges, CYC	Good
72	F	Our series	CryoVas	Yes	Arthralgia, purpura, ENT signs, pulmonary oedema, heart murmur, AKI, hematuria, proteinuria	Bartonella spp serology	Low C3/C4, cryoglobulinemia, RF	Endocapillary GN with immune complexes	Tazocillin, Rovamycin, Gentamicin	-	Good
55[8]	M	Literature	AAV	Yes	Fatigue, fever, pulmonary oedema, AKI, proteinuria, hematuria	B. Henselae serology	Anti-PR3, low C3, RF	Pauci-immune crescentic GN	Doxycycline, Rifampicin, Gentamicin	GC	Good
36[24]	F	Literature	AAV	Yes	Fever, arthralgia, heart murmur, purpura, myalgia, AKI, hematuria, proteinuria	B. Henselae serology + Aortic valve culture	Anti-PR3, RF	Pauci-immune crescentic GN	Doxycycline, Gentamicin	GC, CYC, AZA, MMF	Good
47[9]	M	Literature	AAV	Yes	Fever, pulmonary oedema, heart murmur, AKI, hematuria, proteinuria	B. Henselae aortic valve culture	Anti-PR3	Crescentic GN with immune complexes	Doxycycline, Rifampicin	-	Good
42[11]	F	Literature	AAV	Yes	Fever, heart murmur, AKI, proteinuria	B. Henselae serology + aortic valve PCR	Anti-PR3, anti-MPO, AAN, low C3, RF	Proliferative GN with immune complexes	Doxycycline, Gentamicin, Ceftriaxon	GC	Good
43[14]	M	Literature	AAV	Yes	Fever, AKI, hematuria	B. Henselae serolgy + valve PCR	Anti-PR3	Crescentic GN with immune complexes	Doxycycline, Gentamicin	GC, CYC	Good
74[15]	M	Literature	AAV	Yes	Fatigue, splenomegalia, AKI, proteinuria	B. Henselae serology	Anti-PR3, low C3/C4	Endocapillary proliferative GN	Clarithromycin, Gentamicin	GC, CYC	Good
64[17]	F	Literature	AAV	Yes	Fever, arthralgia, myalgias, mononeuropathy multiplex, AKI	B. Bacilliformis blood culture	p-ANCA, RF	Interstitial nephritis	Gentamicin, Ciprofloxacin, Rifampicin	GC, AZA	Good
67[18]	M	Literature	AAV	Yes	Fatigue, AKI, hematuria, proteinuria	B. Henselae serology + aortic valve PCR	Anti-PR3, Anti-MPO, low C3, RF	Crecentic GN with immune complexes	Doxycycline, Rifampicin	GC, CYC	Good
68[7]	M	Literature	AAV	Yes	Fever, AKI, hematuria, proteinuria	B. Henselae serology + aortic valve PCR	Anti-PR3	Crescentic GN with immune complexes	Doxycycline, Gentamicin	GC, CYC	Good
18[10]	F	Literature	AAV	Yes	Fever, heart murmur, AKI, proteinuria, hematuria	B. Henselae blood PCR	Anti-PR3, low C3/C4	Membranous and crescentic GN with immune complexes	Not mentioned	GC	Unkown
64[16]	M	Literature	AAV	Yes	Purpura, heart murmur, AKI, hematuria, proteinuria	B. Quintana serology + aortic valve PCR	Anti-PR3, AAN, RF, low C3	Focal glomerular sclerosis without proliferation, mild interstitial inflammation	Doxycycline, Ceftriaxon, Gentamicin	-	Good
61[20]	M	Literature	AAV	Yes	Fever, purpura, AKI, proteinuria	B. Henselae serology + aortic valve PCR	Anti-PR3	Extra-, endo- and mesangial proliferative GN with immune complexes	Doxycycline	-	Good
74[21]	M	Literature	AAV	Yes	Fever, pulmonary oedema, AKI, hematuria, proteinuria	Bartonella sp serology	Anti-PR3, low C3/C4	Crescentic GN with immune complexes	Doxycycline, Gentamicin	-	Good
78[22]	F	Literature	AAV	Yes	Fatigue, arthritis, AKI, proteinuria	B. Henselae serology	Anti-PR3, AAN, low C3	Endo- and extracapillary GN with immune complexes	Doxycycline	-	Good
45[12]	M	Literature	AAV	No	Fever, purpura, hepatosplenomegaly, AKI	Lymph node PCR	p-ANCA	Lymph node abscess Pauci-immune crescentic GN	Azithromycin	-	Kidney graft loss

48[13]	M	Literature	CryoVas	Yes	Pulmonary oedema, heart murmur	B. Quintana serology + blood PCR	Cryoglobulinemia, low C3/C4	Crescentic and membranous GN without immune complexes	Doxycycline, Rifampicin	GC, Plasmatic exchanges	Good
65[19]	F	Literature	IgA vasculitis	No	Necrotic purpura, AKI, proteinuria, hematuria	B. Henselae serology	-	Skin leukocytoclasic vasculitis Mesengial GN with IgA deposition	Azithromycin	GC	Good
6[23]	F	Literature	Leukocystoclastic vasculitis	No	Fever, arthralgia, purpura	B. Henselae serology	-	Skin leukocytoclastic vasculitis with immune complexes Granulomatous adenopathy	Rifampicin	-	Good

AAV : ANCA-associated vasculitides ; CryoVas : cryoglobulinemia vasculitis ; RF : rheumatoid factor ; AAN : anti-nuclear antibody ; GC : glucocorticosteroids ; CYC : cyclophosphamid ; AZA : azathioprin ; MMF : mycophenolate mofetil ; GN : glomerulonephritis ; LFU : lost to follow up ; AKI : acute kdiney injury

Table 2 : Case description of vasculitides caused by Coxiella infections

Age	Sex	Case origin	Mimicked Vasculitis	Endocarditis	Clinical findings	Phase	Immunology workup	Pathological findings	Antibiotic treatment	Immuno-suppressors	Outcome
Small vessel vasculitis											
61	M	Our series	CryoVas	Yes	Fever, purpura, adenomegaly, splenomegaly	Chronic	Cryoglobulinemia, ANCA, APLA, monoclonal IgG lambda	Skin leucocytoclastic vasculitis	Hydroxychloroquine, Doxycyclinee	-	Good
60	M	Our series	CryoVas	No	Hematuria, nephrotic syndrome, AKI	Acute	Cryoglobulinemia, APLA	-	Hydroxychloroquine, Doxycyclinee	-	LFU
55	F	Our series	CryoVas	No	Fever, purpura	Acute	Cryoglobulinemia	-	Hydroxychloroquine, Doxycyclinee	-	Good
80	F	Our series	CryoVas	Yes	Asthenia, lower limbs edema	Chronic	Cryoglobulinemia	Endocapillary and crescentic GN	Hydroxychloroquine, Doxycyclinee	GC, RTX	Good
43	M	Our series	AAV	Yes	Fever, necrotic purpura, adenomegaly	Chronic	ANCA anti-PR3	Positive IF (skin)	Hydroxychloroquine, Doxycyclinee	-	Good
73[34]	M	Literature	AAV	Yes	Fever, myalgia, arthralgia, proteinuria, AKI	Chronic	ANCA anti-PR3	Pauci-immune crescentic GN	Hydroxychloroquine, Doxycyclinee	GC, CYC, RTX	Good
64[3]	M	Literature	CryoVas	No	Fever, arthralgia, hepatomegaly, proteinuria	Acute	Cryoglobulinemia, APLA	Fibrin ring granuloma (liver)	Doxycyclinee	-	Good
47[35]	F	Literature	CryoVas	Yes	Asthenia, arthralgia, purpura, hepatosplenomegaly	Chronic	Cryoglobulinemia, low complement	Positive IF (skin)	Tetracycline	-	Good
66[36]	M	Literature	CryoVas	Yes	Asthenia, fever, purpura, hepatomegaly	Chronic	Cryoglobulinemia	Granuloma (liver)	Doxycyclinee, Ofloxacine	GC	Good
54[37]	F	Literature	CryoVas	Yes	Livedo, asthenia	Chronic	Cryoglobulinemia, RF	Negative TAB and muscular biopsy	Hydroxychloroquine, Doxycyclinee	-	Good
69[38]	M	Literature	CryoVas	Yes	Asthenia, proteinuria, hematuria	Chronic	Cryoglobulinemia	Membrano-proliferative GN	Hydroxychloroquine, Doxycyclinee	-	Good
65[39]	F	Literature	CryoVas	Yes	Fever, purpura, hepatosplenomegaly, AKI, proteinuria	Chronic	Cryoglobulinemia, RF, low complement	-	Hydroxychloroquine, Doxycyclinee	GC	Good
71[40]	M	Literature	CryoVas	Yes	Purpura, neuropathy, ischemic colitis	Chronic	Cryoglobulinemia, RF, APLA, low complement	-	Hydroxychloroquine, Doxycyclinee	GC, RTX	Good
64[41]	M	Literature	CryoVas	No	Fever, purpura, anemia	Chronic	Cryoglobulinemia, monoclonal IgG kappa	-	Hydroxychloroquine, Doxycyclinee	-	Good
55[42]	M	Literature	LCV	Yes	Purpura, hepatosplenomegaly	Chronic	RF, monoclonal IgG kappa	Skin leucocytoclastic vasculitis Infectious hepatitis	Hydroxychloroquine, Doxycyclinee	-	Good
41[43]	M	Literature	LCV	No	Fever, abdominal and bone pain, purpura	Chronic	Low complement	Skin leucocytoclastic vasculitis	Doxycyclinee	-	LFU
Medium vessel vasculitis											
72[3]	F	Literature	PAN	No	Fever, myalgia	Chronic	-	Hepatic aneurysm	Hydroxychloroquine, Doxycyclinee	-	Good
Large vessel vasculitis											
72[44]	M	Literature	GCA	No	Fever, asthenia, abdominal pain	Chronic	-	Lymphoplasmocytic infiltrate and rare giant cells on aorta	Hydroxychloroquine, Doxycyclinee	GC	Good
60[45]	F	Literature	GCA	No	Asthenia, fever, headache	Acute	ANA, APLA	Negative TAB	Hydroxychloroquine, Doxycyclinee	GC	Good
64[46]	M	Literature	GCA	No	Fever, abdominal pain	Acute	-	Granulomatous infiltrate and giant cells, IEL fragmentation	Tetracycline	GC	Good
50[3]	F	Literature	Takayasu	No	Fever, right arm pain	Chronic	-	Negative TAB and muscular biopsy	Hydroxychloroquine, Doxycyclinee	-	Death

CryoVas : cryoglobulinemia vasculitis ; AAV : ANCA-associated vasculitides ; PAN: polyarteritis nodosa; GCA: Giant Cell Arteritis AKI : acute kidney injury ; LCV : leucocytoclastic vasculitis ; TAB: temporal artery biopsy ; IEL: internal elastic lamina; ANCA: antineutrophil cytoplasmic antibodies ; APLA: antiphospholipid antibodies ; PR3: proteinase 3 ; RF: rheumatoid factor ; IF: immunofluorescence ; GN : glomerulonephritis ; TAB: temporal artery biopsy ; GC : glucocorticsteroids ; CYC: cyclophosphamide ; RTX: Rituximab ; LFU : lost to follow-up.

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