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Review

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Nonviral cryoglobulinemic vasculitis: an updated review for clinical practice

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Abstract

The clinical spectrum of cryoglobulinemic-associated diseases is broad and heterogeneous, with manifestations ranging from mild symptoms (e.g., isolated palpable purpura) to organ- and life-threatening involvement (e.g., membranoproliferative glomerulonephritis). Cryoglobulins are classified into three types. Type I cryoglobulinemia consists of one monoclonal immunoglobulin (Ig) and is practically always associated with B-cell lymphoproliferative disorders. In contrast, type II/III (mixed) cryoglobulinemia is composed of mono- or polyclonal IgM with rheumatoid factor activity bound to polyclonal IgG. Since the introduction of more efficient therapies for chronic hepatitis C virus (HCV), other diseases such as systemic autoimmune disorders and lymphoproliferative neoplasms have been established as the main causes of mixed cryoglobulinemic vasculitis. The pathogenesis of cryoglobulinemic vasculitis is a complex multifactorial process that involves B-cell aberrant lymphoproliferation and autoantibody production. Therefore, treatment of these patients may involve not only measures aimed to mitigate the severity of clinical manifestation but also those that address the associated underlying disease responsible for Ig production. The treatment of patients with type I cryoglobulinemia is primarily focused on controlling B lymphocyte clones responsible for cryoglobulin production, mostly with chemotherapy drugs.

Treatment of mixed cryoglobulinemia syndrome is based on rituximab plus glucocorticoids, which induces remission in the vast majority of cases. In the rare patients that do not respond to rituximab administration, potential rescue approaches include alkylating agents, biologic therapies, conventional immunosuppression, and plasma exchange, although with partial efficacy. This narrative review explores the etiology, pathophysiology, clinical manifestations, treatment, and prognosis of nonviral cryoglobulinemic disease. A special focus is placed on the treatment of type I cryoglobulinemia and rituximab-resistant non-HCV cryoglobulinemic vasculitis.

Keywords: Vasculitis, cryoglobulinemia, rituximab

INTRODUCTION

Cryoglobulins are abnormal circulating immunoglobulins (Ig) that precipitate at low temperatures and resolubilize when rewarmed[1]. The term cryoglobulinemia refers to the persistent presence of cryoglobulins in serum[1]. Cryoglobulinemic vasculitis (cryoV) is the clinical syndrome of cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and is associated with cryoglobulins in serum, resulting in end-organ damage in the skin, peripheral nerves, and glomeruli[2,3].

Cryoglobulins can be classified on the basis of cryoprecipitate characteristics, that is, Ig isotype and composition[4,5]. The classification, proposed by Brouet *et al.* in 1974, includes three major types that correlate clinical features with pathogenicity[4,6]. Type I cryoglobulins are characterized by a single monoclonal Ig (either IgG or IgM, rarely IgA isotype), type II combines a monoclonal IgM with rheumatoid factor activity (RFA, less commonly IgG or IgA) and polyclonal immunoglobulins, while type III cryoglobulins consist of a mixture of polyclonal Ig, most frequently of IgG and IgM isotypes, although IgA can also be associated[4,6]. Cryoglobulins of types II and III are collectively known as mixed cryoglobulins.

The treatment of patients with cryoV depends on the associated underlying disease, the severity of clinical manifestations, and the potential end-organ damage. In previous decades, hepatitis C virus (HCV) was the leading cause of cryoglobulinemia worldwide, accounting for 70%-90% of mixed cryoglobulins[7-9]. However, the introduction of new direct-acting antiviral (DAA) agents has dramatically reduced the predominance of HCV as the main etiologic agent of cryoV and shifted it in favor of other causes such as systemic autoimmune diseases, lymphoproliferative neoplasms, and the so-called "essential" cryoglobulinemia[8,10].

Although treatment regimens for cryoglobulinemic disease secondary to HCV have been extensively investigated and are well established[11,12], limited information is available on the management strategies of patients with HCV-unrelated cryoV. As the epidemiology of cryoglobulinemic vasculitis is evolving, and the disease remains a challenge owing to the heterogeneous underlying associations and the occurrence of organ and life-threatening presentations[13-15], the present review will develop into the etiology, pathophysiological mechanisms, clinical characteristics, management, and prognosis of cryoV. Special emphasis is placed on the treatment of type I cryoglobulinemia and therapeutic options in the setting of cryoV patients who are refractory to rituximab.

Literature review

A PubMed, Embase, and Cochrane Central search was done (up to June 2023). The search strategy included the following key terms: cryoglobulinemia, cryoimmunoglobulinemia, vasculitis, immune complex vasculitis, and mixed cryoglobulinemic vasculitis in combination with refractory, resistant, rituximab, treatment, therapy, and management.

ETIOLOGY

Within the three major groups of cryoglobulinemia, type I accounts for 10%-22% of all cases, while mixed cryoglobulinemia is responsible for 80%-85%, with type II cryoglobulins being the most frequent type[1,16-19]. Although the list of diseases associated with the production of cryoglobulins is extensive, in clinical practice, they usually belong to one of three main causative groups, i.e., infections, autoimmune diseases, and B-cell lymphoproliferative disorders[1,20,21]. The term "essential" or "idiopathic" cryoglobulinemia is used to designate a small percentage of cases where an etiologic factor remains unidentified[1,2,21].

Type I cryoglobulinemia

Type I cryoglobulins are always associated with B-cell lymphoproliferative disorders, either with malignant or indolent characteristics. Overall, IgG isotype is more frequent than IgM, presenting in approximately 60% and 40% of cases, respectively[16-18]. According to data from large observational cohort studies, a lymphoproliferative disorder was diagnosed in more than 90% of patients with type I cryoglobulins, with monoclonal gammopathy of undetermined significance (MGUS) identified in 36%-86% of patients, and an overt hematological malignancy found in 20%-64%[16-18,22,23]. In these studies, Waldenström macroglobulinemia (WM, 18%-33%) and multiple myeloma (MM, 11%-20%) were the most commonly diagnosed malignant neoplasms[16-18,22,23]. Less common causes of monoclonal cryoglobulinemia include chronic lymphocytic leukemia, hairy cell leukemia, or Hodgkin's and non-Hodgkin's lymphomas (NHL)[5,16-18,22,23]. The association with solid neoplasms is extremely rare[24].

Type II/III (mixed) cryoglobulinemia

Historically, chronic HCV infection was the main cause of mixed cryoglobulinemia, while autoimmune disorders, B-cell lymphoid malignancies, other infectious diseases, and essential cryoglobulinemia accounted for a small fraction of the cases[1,8,10,25-27]. This has changed in recent years, as the use of DAA for the treatment of HCV progressively led to a decline in the occurrence of HCV-related mixed cryoglobulinemia and the rise of autoimmune diseases as the most frequent conditions associated with the onset of cryoV[8].

Systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS) are the most frequent systemic autoimmune diseases associated with mixed cryoglobulinemia and cryoV[1,3,5,8,19,25-27]. Type II/III cryoglobulins have been reported in 10%-25% of patients with SLE and 5%-20% with SS, although the percentage of symptomatic individuals showing cryoV is considerably lower[5-7,28-32]. The presence of type II cryoglobulins in primary SS is an important prognostic factor, as it has been associated with extra-glandular involvement, systemic vasculitis, and more importantly, increased risk of developing B-cell lymphomas and higher mortality[28-30,33]. Given its relevance for clinical management, the detection of persistent mixed cryoglobulinemia and vasculitis symptoms, principally affecting the skin and peripheral nervous system, should alert for the development of lymphoid malignancies in individuals with SS[28,29]. In other autoimmune diseases, such as systemic sclerosis and rheumatoid arthritis, cryoglobulins can be identified approximately in 3%-10% of patients[19,26,34], while their detection in inflammatory myopathies, sarcoidosis, primary biliary cirrhosis, and autoimmune thyroiditis remains anecdotical[5,21,30,35].

Non HCV-related infectious mixed cryoglobulinemia may be secondary to viruses, bacteria, parasites, or fungus[10,25,35]. In particular, 2%-5% of cases of mixed cryoV are attributable to hepatitis B virus (HBV) infection[5,36]. As viral suppression may induce remission of cryoV manifestations, antiviral therapy with nucleot(s)ide analogs such as entecavir or lamivudine is considered the mainstay treatment for HBV-related cryoV[10,37-43], while the addition of glucocorticoids and rituximab may be considered in patients with moderate to severe manifestations (recently reviewed in[41-43]). An association of type II/III cryoglobulinemia

and other viruses, for example, cytomegalovirus, Epstein-Barr virus, adenovirus, parvovirus B19, and human immunodeficiency virus, has also been suggested in previous studies[5,44,45]. With regard to bacterial infections, case reports of subacute endocarditis, syphilis, Lyme disease, and brucellosis, among others, have been published[1,3,5,19,25-27,46]. Occasionally, parasitic and mycotic infections have also been identified as potential causes of mixed cryoglobulinemia, such as leishmaniasis, toxoplasmosis, and coccidioidomycosis[1,3,5,19,25-27,47].

The presence of cryoglobulinemia, mainly of type II, may also be indicative of an underlying hematological disorder. In this sense, B-cell malignancies may include B-cell non-Hodgkin's lymphomas such as marginal zone lymphoma, diffuse large B-cell, and follicular lymphoma, as well as lymphoplasmacytic lymphomas[1,3,5,19,25-27,35,48]. Solid cancers, e.g., thyroid, lung, liver, breast, nasopharynx, and esophagus, are an uncommon cause of the disease.

PATHOPHYSIOLOGY

The pathogenesis of cryoV is a complex multifactorial process that involves environmental factors, polygenic host susceptibility, and B-cell immune dysregulation[49-53]. The hypothetical sequence of pathogenic events leading to the development of organ damage in cryoV begins with the production of cryoglobulins in predisposed individuals[49-53]. Once cryoglobulins have emerged, they exert their pathogenic effect by two major mechanisms, that is, precipitation in the microcirculation and deposition of immune complexes in small vessels[20].

Genesis of cryoglobulins

The process leading to the development of cryoglobulins has been extensively investigated in HCV, but data is limited for nonviral cryoglobulinemia[5]. Based on the model of HCV, it has been suggested that the emergence of mixed cryoglobulins is the consequence of aberrant autoantibody production due to sustained chronic antigenic stimulation (e.g., by viral particles or Ro/La self-ribonucleoproteins) of a limited pool of autoreactive B cells[1,5]. In this hypothetical cascade of events, the constant stimulation of B lymphocytes results in gradual and progressive proliferation and increased cellular activation[54-57]. The persistence of the antigenic stimulus initially gives rise to polyclonal low-affinity, benign RF antibodies, which are later substituted by monoclonal antibodies with improved affinity for self-IgG molecules, harboring stereotypic combinations of Ig heavy and light chain genes (Wa and Po idiotypes)[1,5,20,58-66]. In the case of HCV, RF specificity of monoclonal RF cryoglobulins is acquired by somatic hypermutation of B-cell clones, 60%-80% related to the WA crossidiotype (XId) and 7% of PO XId[67-70]. The third step in this sequence is cell proliferation and clonal expansion favored by driver mutations in genes recurrently mutated in lymphomas and leukemias (e.g., activation-induced cytidine deaminase), which allows newly formed B cells to evade tolerance checkpoints. Importantly, as clonal expansion reaches a critical threshold, this process may become self-sustaining, because exposure even to small amounts of any antigen-antibody complex would progressively boost RF synthesis. The final event in the cascade, which precipitates the conversion of benign RF antibodies to pathogenic ones able to induce cryoprecipitation and vasculitis, is the accumulation of V(D)J mutations that reduce protein solubility of autoantibody-antigen complexes[65,70-73]. Of relevance, the overstimulation of B-cell clones and accompanied immune dysregulation may not only be involved in the development of cryoglobulins but also in the progression to secondary malignancies, a late complication that may be observed in patients with mixed cryoglobulinemia. Lastly, although the pathogenic mechanisms involved in the production of type I cryoglobulins are not fully understood, it may be hypothesized that this is also initiated by chronic stimulation of B cells by ubiquitous self-antigens, probably of hematological origin. Then, through the processes described earlier, that is, progressive clonal selection, accumulation of somatic mutations, and overexpression of lymphomagenesis-related genes, autoreactive secretory B-cell

clones finally exert their noxious effects by secreting pathogenic monoclonal cryoglobulins[5,20,74].

Tissue injury

The pathogenic role of cryoglobulins in organ and tissue damage is associated with cryoglobulin aggregation, vessel occlusion, and hyperviscosity in type I cryoglobulinemia, and immune complex-mediated vasculitis in the case of mixed cryoglobulins[19,20,75].

Type I monoclonal cryoglobulins are not effective activators of inflammatory mediator systems and, therefore, rarely cause overt vasculitis. In contrast, the morbidity of this type of cryoglobulins is primarily induced by aggregation, crystallization, and precipitation of monoclonal immunoglobulins within small- and medium-sized vessels, with the resultant mechanical occlusive vasculopathy[5,15,75,76]. Although the mechanism of type I cryoglobulin aggregation is not fully understood, numerous interrelated factors seem to be of relevance, for example, temperature, pH, decreased solubility, Ig hydrophobic amino acid substitutions, amount of galactose and sialic acid residues, cryoprecipitate morphology structure, rheology of the local circulation, and isotype concentration (IgM > IgG)[1,5,6,19,20,76-89]. The complement system may also exert additional vessel damage by bounding to type I cryoglobulin aggregates[77,78,90]. On rare occasions, a high concentration of circulating monoclonal cryoglobulins leads to increased blood viscosity and severe tissue hypoperfusion, mostly in patients with WM and MM[5,15].

Mixed cryoglobulinemia, on the other hand, causes a true immune complex-mediated vasculitis[1]. The pathogenetic mechanism underlying the development of vascular inflammation involves the enhanced formation of cryoglobulin-containing immune complexes. A decrease in temperature then leads to an increase in immune complex concentration and size, favoring their precipitation in small arteries and capillaries[5,6,75,76,88,91]. Cryoprecipitation in mixed cryoglobulinemia depends on the formation of circulating and *in situ* immune complexes that are induced by the binding of monoclonal IgM molecules, usually with RFA, to polyclonal IgG and complement fractions[3,5,7,20,88,92]. These large cryoglobulin aggregates are able to remain free in circulation due to impaired clearance and are then deposited on vascular endothelium, where they trigger vascular inflammation[3,5,7,15,76,85,91,93,94]. The presence of immune complexes in blood vessels, the constant influx of inflammatory leukocytes (mostly lymphocytes and macrophages), fixation of complement fractions to cryoglobulin-containing immune complexes and aggregates, and local activation of the classical pathway of complement converge to induce microvascular injury and overt vasculitis[5,15,95-101]. In contrast to cutaneous vasculitis and other cryoglobulinemic manifestations induced by protein precipitation at low temperatures, renal damage is not due to a decrease in temperature, as the physiological temperature of the kidney is 37 °C, and it is maintained even in extreme weather. Therefore, pathophysiological mechanisms affecting the glomeruli appear to combine a sudden increase in cryoglobulin concentration (due to ultrafiltration) with modifications of the ionic strength by ion exchange, thus resulting in cryoglobulin aggregation and their deposition on the glomerular membrane[86,102,103]. Of relevance, cryoglobulins containing monoclonal Ig (types I and II) are more frequently associated with kidney damage, such as membranoproliferative glomerulonephritis, than type III.

The characteristics of the cryoprecipitate, such as temperature, Ig glycosylation, solubility, and organ concentration, among other and local environmental factors, influence the propensity of cryoglobulin to form immune complexes and, thus, their capacity to develop vascular lesions[1,19,91,102,104-107]. Of relevance, type III cryoglobulins are less frequently associated with cryoV manifestations (than type II cryoglobulinemia) because they tend to induce smaller immune complexes due to a less effective RFA of polyclonal immunoglobulins[76,108].

PATHOLOGICAL FEATURES

Cryoglobulinemic vasculitis is characterized histologically by the presence of moderate to marked inflammation of the vessel wall in association with cryoglobulin and complement deposits[2]. CryoV affects predominantly small-sized vessels that are within organs and tissues[2,75]. Frequent examples include dermal postcapillary venules, glomerular capillaries, epineural arterioles, and rarely other small arteries[2,36,75,109-111]. Medium-sized arterial involvement is uncommon, with less than 20% of patients presenting with lesions of polyarteritis nodosa type[1,2].

In leukocytoclastic vasculitis, the histopathological hallmark of purpuric lesions associated with cryoV, acute inflammatory infiltrate is composed predominantly of polymorphonuclear neutrophils, while older lesions can demonstrate lymphocytic infiltration. In contrast to anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, cryoV may be associated with less destructive vascular wall lesions, few fibrinoid necrosis, fewer neutrophils, and predominance of lymphocytes and monocytes mainly located in the perivascular space[1]. Granular deposits of IgM, IgG, and complement fractions are typically observed by immunofluorescence microscopy. Nerve biopsies typically display a mononuclear inflammation localized in the perivascular epineurium space[111,112]. In type I cryoglobulinemia, the main pathologic characteristics are those associated with the presence of luminal noninflammatory hyaline thrombi, that is, aggregates composed of cryoglobulins and complement usually identified in skin or kidney lesions[109-111]. In the setting of type I cryoglobulinemia, bone marrow biopsies may show features of the underlying malignant hemopathy.

Kidney involvement associated with cryoV is characterized by type I membranoproliferative glomerulonephritis (MPGN) in approximately 70%-80% of patients. This inflammatory glomerulonephritis has been mostly associated with the presence of type II cryoglobulinemia with IgM *kappa* with RFA[113]. Pathologic characteristics [Figure 1] include dense mesangial cell proliferation, abundant cellular glomerular infiltrates of monocytes and macrophages, intracapillary hyaline thrombi, and thickening of the glomerular basement membrane. Diffuse IgM deposition in the capillary loops detected by immunofluorescence microscopy and subendothelial dense deposits identified by electron microscopy are also typical[5,75,114-117]. A small fraction of kidney specimens present with endocapillary proliferative glomerulonephritis[114,117].

CLINICAL MANIFESTATIONS

The clinical expression of cryoglobulin-related disease is highly variable, ranging from mild symptoms to fulminant organ- and life-threatening complications[21,118,119].

Type I cryoglobulinemia

The main clinical manifestations of type I cryoglobulinemia are that resultant from an occlusive vasculopathy [Table 1] and those related to the burden of the underlying B-cell lymphoproliferative disease[5,19,76,88]. True vasculitis is rarely observed[3].

The skin is the most frequent organ affected in patients with monoclonal cryoglobulinemia[16-18]. Cutaneous involvement is presented as multiple purpuric petechias, which are located on dependent surfaces. Other skin manifestations such as livedo reticularis, necrotic unhealing ulcers, digital gangrene, or cold-induced vasomotor symptoms, e.g., acrocyanosis or Raynaud phenomenon may also be observed [Table 1 and Figure 2][13,16-19,25]. Characteristically, cold-induced features are often confined to acral sites, i.e., the nose, ears, and toes[17-19]. Extra-cutaneous disease may include constitutional symptoms such as fatigue, fever, and arthralgia, sensory peripheral neuropathy, which mostly affects the lower limbs, and kidney involvement

Table 1. Frequency of major organ involvement in type I and mixed cryoglobulinemia

	Type I cryoglobulinemia[16-18,20,25]	Type II/III (mixed) cryoglobulinemia[20,25,35,121,241]
General symptoms		
Fatigue	7%-15%	70%-90%
Fever	5%-8%	NA
Arthralgia	12%-24%	30%-80%
Arthritis	8%	< 10%
Skin involvement	69%-86%	70%-85%
Purpura	25%-69%	40%-98%
Raynaud phenomenon	18%-21%	20%
Ulcers or skin necrosis	27%-35%	13%-17%
Cold-induced symptoms	90%-100%	0%-10%
Livedo reticularis	13%-18%	< 10%
Neurological involvement		
Peripheral neuropathy	14%-32%	25%-75%
Central nervous system disease	3%	5%-10%
Kidney involvement	13%-30%	11%-35%
Gastrointestinal involvement	NA	2%-5%
Cardiac involvement	NA	< 5%
Pulmonary involvement	NA	< 5%
Hyperviscosity syndrome	5%	2%

NA: Have been reported, but appear to be a very uncommon manifestation. Adapted from[1].

consisting of proteinuria, microscopic hematuria, hypertension, and/or increased creatinine levels [Table 1][16-18,23,25]. These manifestations may precede the diagnosis of an overt hematologic cancer by months to years[1].

Hyperviscosity syndrome is a particular complication of type I cryoglobulinemia that ensues as a result of plasma volume expansion in patients with an elevated concentration of circulating high-molecular-weight monoclonal Igs. The syndrome is characterized by a myriad of signs and symptoms: headache, mental confusion, dizziness, somnolence, sudden hypoacusia, blurred vision or visual loss, recurrent epistaxis, mucosal bleeding, and heart failure[3,16,18,25,26,120].

Type II/III (mixed) cryoglobulinemia

Mixed cryoglobulinemia manifests typically as a systemic immune complex-mediated vasculitis with C4 hypocomplementemia. Type II cryoglobulins are characteristically more pathogenic than type III cryoglobulinemia and are associated with increased prevalence of skin, peripheral nerve, and kidney features[121]. Table 1 shows the frequency of major clinical manifestations associated with mixed cryoV.

Most patients exhibit general symptoms, that is, severe fatigue, myalgias, and weight loss[20,25,35,113,121]. Arthralgias are common and usually present in a nonmigratory, symmetric, and bilateral distribution, which predominantly affects the hands, wrists, knees, and ankles[1,113]. Mild non-erosive arthritis is rarely reported[1,3,26,113,122-124]. The prevalence of constitutional symptoms such as fever, weakness, myalgia, and arthralgia is more prevalent in patients with mixed cryoglobulinemia than in those with type I cryoglobulin-related disease[3].

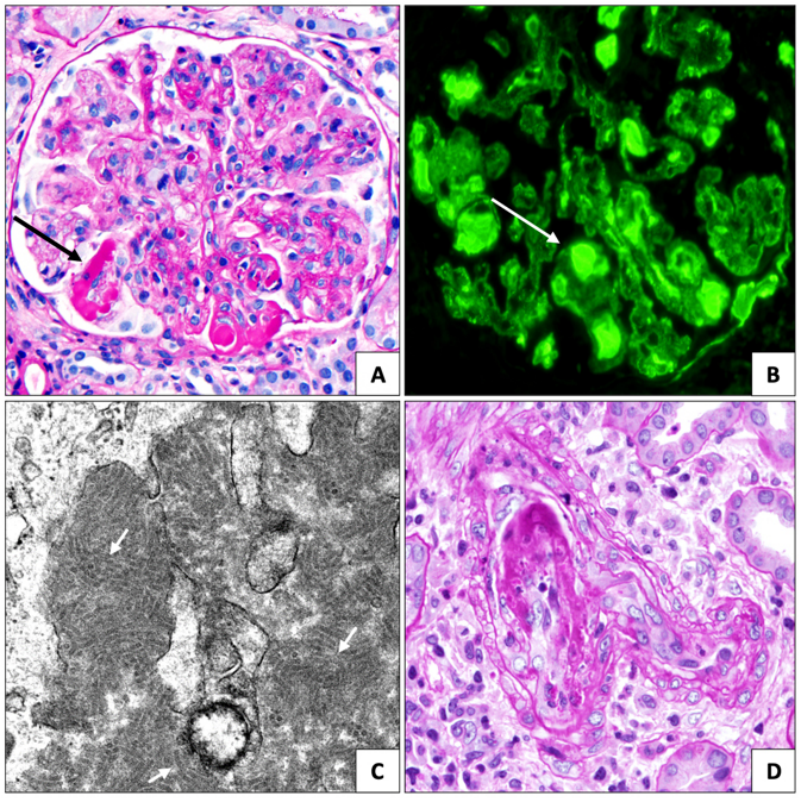

Figure 1. Pathologic features of kidney involvement in cryoglobulinemic vasculitis. (A) Cryoglobulin-related glomerulonephritis with a membranoproliferative pattern of injury showing multiple hyaline thrombi (black arrow) (light microscopy, periodic-acid-Schiff stain). (B) Cryoglobulinemic glomerulonephritis with multiple hyaline thrombi staining positive for C3 (white arrow). The glomerulus also has capillary wall and mesangial granular staining (immunofluorescence microscopy, FITC anti-C3). (C) Electron microscopy demonstrating short 35 nm microtubules (white arrows) in parallel arrays within the immune deposits in the glomerulus. (D) Arteritis in a small interlobular artery with intraluminal hyaline material, endothelial swelling, and transmural and perivascular inflammation (light microscopy, periodic-acid-Schiff stain). Images courtesy of Dr. J Charles Jennette, University of North Carolina at Chapel Hill, NC, USA.

Palpable purpura [Figure 2] represents the most common manifestation and may be the first sign of the disease[20,25,35,121]. It predominantly affects the lower extremities and typically heals leaving brownish postinflammatory hyperpigmentation, due to hemosiderin deposition. Clinical episodes are usually intermittent, relapsing, and may vary from mild isolated purpuric papules and erythematous macules to extensive coalescent necrotic areas that may become ulcerated[36,113,125-128]. Relapses are usually associated with protracted standing, cold exposure, drugs, or infections[4,26]. Although livedo reticularis, Raynaud's syndrome, acrocyanosis, and cutaneous necrosis may occur, they are less frequent than in type I cryoglobulinemia [Figure 2][1]. Of relevance, cutaneous features may precede extracutaneous involvement by several years.

Cryoglobulinemic vasculitis most commonly affects the nervous system in the form of distal sensory or sensorimotor polyneuropathy or mononeuritis multiplex. Polyneuropathy is the most frequently described form of neurologic involvement. As purpura, it can also be part of the inaugural disease manifestations. Generally, it is presented as slowly progressive, neuropathic pain with a burning sensation and asymmetric paresthesia, mainly affecting the lower limbs[129-132]. Motor impairment is uncommon initially but may develop as a late complication[1,12,113]. Electromyography studies reveal an axonal, sensorimotor neuropathy that usually affects the peroneal and sural nerves[13,133,134]. Central nervous system (CNS) disease is a rare but

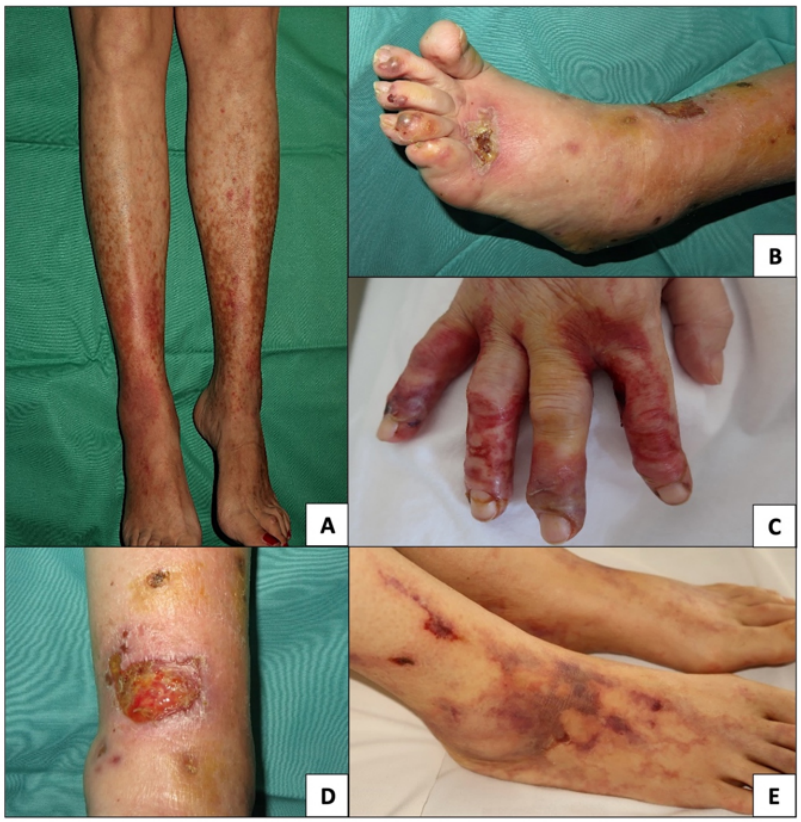

Figure 2. Cutaneous manifestations of cryoglobulinemic vasculitis. (A) Orthostatic purpura rash involving the lower extremities. Purpuric lesions show diverse phases of evolution, combining more acute (erythematous macules) and residual (brownish) hyperpigmentation. (B) Hemorrhagic blisters and skin ulcers with central necrotic tissue. (C) Distal ischemia and digital necrosis of fingers in severe cryoglobulinemic disease. (D) Cutaneous vasculitis complicated with painful skin ulcer, located at the ankle. (E) Retiform purpura, a rare manifestation of cryoglobulinemia, consisting of branching, nonblanching patch or plaque, usually indicating concomitant small and medium-vessel involvement.

devastating complication. The most common presentation is ischemic stroke, although acute or subacute encephalopathy, headache, myelitis, seizures or epilepsy, cognitive impairment, or cranial nerve impairment have been reported[1,3,13].

Kidney involvement, a late manifestation that affects one-third of patients, is a marker of worse prognosis, as it has been associated with increased mortality[25,36,127]. Manifestations range from asymptomatic proteinuria and microscopic hematuria (30%-50% of patients) to nephrotic syndrome (20%) or acute renal failure and severe hypertension related to nephritic syndrome (8%-14%)[1,5,12,20,25,35,36,113,115,121,127,135,136]. Factors such as diabetes mellitus, older age, type II cryoglobulins, high serum creatinine levels, and increased proteinuria at diagnosis are associated with worse kidney prognosis and increased risk of death[5,13,97,137]. Must be read progression to chronic kidney disease develops in 10%-15% of cases[36,138,139].

Other manifestations are rare [Table 1]. These include gastrointestinal symptoms such as abdominal pain, gastrointestinal bleeding or perforation, which may occur due to mesenteric vasculitis[1,3,13,20,25,35,113,121,140]. Possible manifestations of cardiac involvement include valvular damage, myocarditis, necrotizing vasculitis of the coronary arterioles resulting in severe congestive heart failure and myocardial infarction, dilated cardiomyopathy, and pericarditis[1,3,13,14,20,25,35,113,121,141,142]. The respiratory system may be involved in the form of diffuse alveolar hemorrhage, interstitial lung disease, and fibrosis[3,13,20,25,26,35,121,143-146]. Lastly, a life-

threatening disease with extensive severe vasculitis may be present in approximately 15% of patients. This form of diffuse, rapidly progressive vasculitis is associated with poor prognosis and high mortality when major organs like the CNS, gastrointestinal tract, lungs, and kidneys are affected[3,14,129].

TREATMENT OF TYPE I CRYOGLOBULINEMIA

Treatment of patients with type I cryoglobulinemia is reserved for symptomatic disease and needs to be individualized, considering the severity of cutaneous and visceral involvement and the underlying triggering hemopathy, as appropriate disease-specific chemotherapy is usually associated with improvement of cryoglobulinemic symptoms [Figure 3][3,5,16-18,22]. As hematological cryoglobulinemia is a complex and potentially fatal disease requiring a combination of anti-inflammatory agents and antineoplastic drugs, close participation and coordination between Hematology/Oncology, Rheumatology, Nephrology, and Internal Medicine specialists is desired and highly needed.

General measures

Patients should be advised to avoid or minimize cold exposure. For example, general measures that may be helpful during activities of daily living include the use of warm clothes in air-conditioned environments, wearing gloves when using the freezer or during ice water manipulation, and temporarily relocating during winter season[3]. Pain relief and wound care, when necessary, should be prioritized[147].

Treatment of cryoV and the underlying hematological malignancy

Due to the low incidence of type I cryoglobulinemic vasculitis and the diverse malignant hemopathies associated with this disease, high-grade evidence detailing the appropriate treatment of type I cryoglobulinemia is lacking; thus, recommendations are mostly based on case series, retrospective observational cohorts, and expert opinion[3,5,16-18,22,23,148]. In addition, the therapeutic approach for patients with cryoglobulinemia associated with a specific underlying B-cell lineage malignancy is largely based on the standard management recommendations of the same B-cell disease without cryoglobulinemia[5]. Therefore, rituximab, bortezomib, lenalidomide, thalidomide, and cyclophosphamide, in association with corticosteroids, are the main therapeutic agents used in this multi-faceted illness[5,16-18,22,23,149-152].

In previous publications, treatment was administered in 65%-88% of individuals with circulating type I cryoglobulins: 80% of the time due to occlusive vasculopathy or vasculitis symptoms and in the other 20% due to clinical manifestations directly related to the hematological malignancy (e.g., peripheral cytopenia, bulky lymphadenopathy, hyperviscosity)[16-18,22,23]. In the remaining patients, no specific chemotherapy was considered as they were asymptomatic, showed only minimal symptoms, or had a low-grade lymphoproliferative abnormality. Based on these studies[16-18,22,23], it appears safe to treat patients with mild symptoms associated with an indolent hematologic disease (e.g., limited palpable purpura, articular involvement, or cold-induced acrocyanosis) using a conservative strategy, which may include cold-prevention general measures, use of non-steroidal anti-inflammatory drugs, and strict follow-up[5,25].

On the other hand, severe cases such as those presented with extensive ulcerative skin disease, severe sensory-motor neuropathy, membranoproliferative glomerulonephritis, or gastrointestinal vasculitis require potent anti-inflammatory agents (e.g., high-dose glucocorticoids), in addition to prompt and specific therapy of the underlying cryoglobulin-producing B-cell disorder. Plasma exchange may be considered especially in organ- or life-threatening conditions[3,5,16-18,22,23].

Previous studies have reported that in cases with MGUS-related cryoglobulinemic vasculitis, high-dose prednisone was the most frequent therapeutic strategy administered[3,5,16-18,25,150]. Second-line therapy mainly

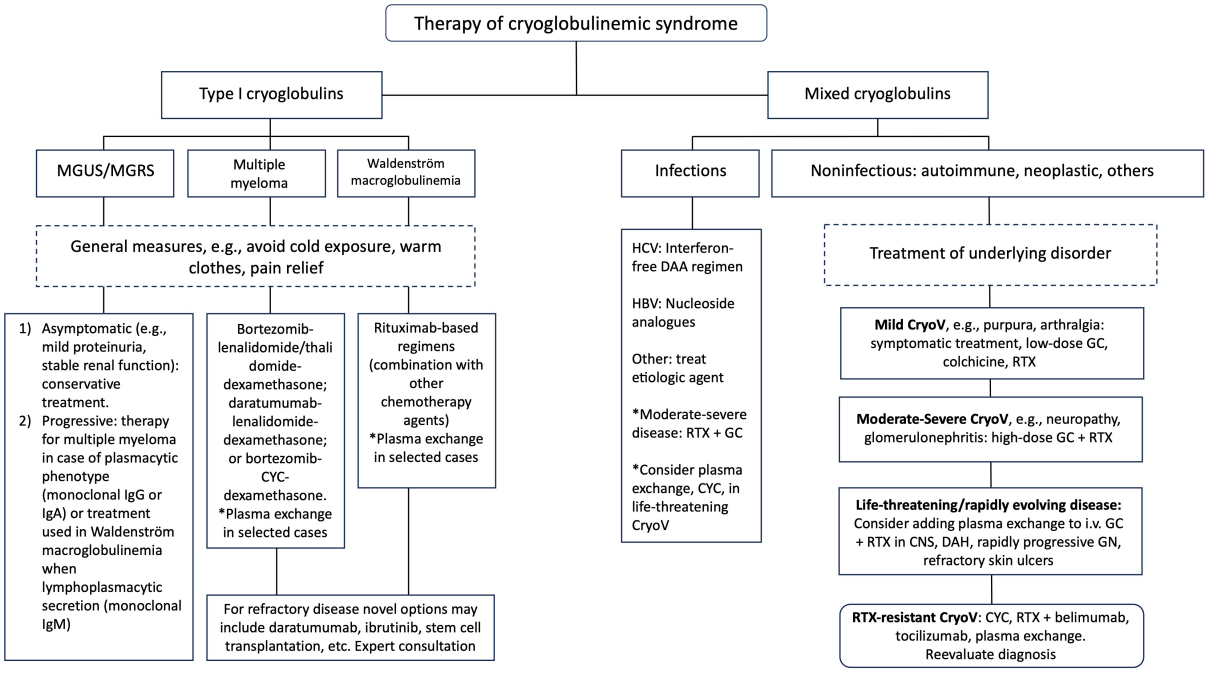

Figure 3. Treatment of cryoglobulinemic vasculitis. In all cases, when an underlying disorder is identified, appropriate disease-specific therapy should be initiated. Plasma exchange is also recommended in cases with symptomatic hyperviscosity syndrome. CNS: Central nervous system; CYC: cyclophosphamide; DAA: direct-acting antivirals; DAH: diffuse alveolar hemorrhage; GC: glucocorticoids; GN: glomerulonephritis; HBV: hepatitis B virus; HCV: hepatitis C virus; MGUS: monoclonal gammopathy of unknown significance; MGRN: monoclonal gammopathy of renal significance; RTX: rituximab.

included rituximab in cases with IgM-secreting MGUS or multiple myeloma drugs when an IgG monoclonal gammopathy is detected[3,5,16-18,25,150]. In these cases, when organ damage is caused directly by the toxicity of monoclonal immunoglobulins, a diagnosis of monoclonal gammopathy of clinical significance should be established[148]. This is particularly important in patients with type I cryoglobulin-associated glomerulonephritis, which has recently been included within the spectrum of manifestations caused by monoclonal gammopathies of renal significance (MGRS)[148]. Specifically, MGRS refers to kidney damage induced by the deleterious effects of monoclonal immunoglobulins secreted by a nonmalignant or premalignant B cell or plasma cell clone[153-155]. In MGRS, the main goal of therapy is to preserve kidney function and avoid the progression of extrarenal manifestations using chemotherapeutic agents targeting the pathologic B-cell clones[153-156]. Although patients with mild proteinuria and stable renal function may not require specific management, those with progressive disease should receive antimyeloma or WM treatment regimens based on a combination of chemotherapeutic agents such as bortezomib, cyclophosphamide, bendamustine, rituximab, thalidomide, lenalidomide, and dexamethasone[153-156]. Very recently, daratumumab, a monoclonal antibody targeting CD38 used for refractory MM[156,157], has shown promising results in a small series of patients with MGRS[158-161].

In patients where MM is the etiologic factor of type I cryoV, bortezomib, thalidomide, and lenalidomide have been reported as the preferred therapeutic options, with an overall efficacy rate of 80%-85%[5,16-18,22,23,25,149-152,162-166]. According to expert consensus recommendations currently proposed for MM without cryoglobulinemia, an induction phase targeting plasma cells with a three-drug regimen using bortezomib, lenalidomide/thalidomide, and dexamethasone; daratumumab, lenalidomide, and dexamethasone; or bortezomib, cyclophosphamide, and dexamethasone, would be indicated as the initial treatment for most patients[167,168]. As bortezomib, thalidomide, and lenalidomide may induce neurotoxic

effects, they should be used carefully in patients with cryoglobulinemia-induced peripheral neuropathy[3,169]. Other reported treatment regimens that have been used for MM-associated cryoV include carfilzomib, pomalidomide, melphalan, bendamustine, alemtuzumab, daratumumab, elotuzumab, and autologous stem cell transplantation[16,17,25,170-172].

In cases with type I cryoglobulinemia in the setting of WM, rituximab (either alone or in combination with other agents) has shown an efficacy rate of 80% when used as a first or second-line treatment[16-18]. This is in line with current international guidelines that recommend a rituximab-based regimen (associated with bendamustine; dexamethasone, and cyclophosphamide; or dexamethasone and proteosome inhibitor, bortezomib) as the initial therapy for symptomatic WM[18,23,169,173-176]. The combination of a nucleoside analog (fludarabine and cladribine) with alkylating drugs (cyclophosphamide and bendamustine) is an alternative option that has been reported in patients with WM-associated cryoglobulinemic vasculitis[17,18,169,176-180]. For patients with refractory WM, ibrutinib has now emerged as a major rescue option[3,175,181,182]. Novel treatment strategies for patients with Waldeström macroglobulinemia may include ofatimumab, a fully anti-CD20 human antibody; inhibition of the AKT/mTOR pathway using everolimus; and MM drugs such as carfilizomib, ixazomib, thalidomide, or lenalidomide[181,183-185]. The identification of WM prognostic somatic mutations by genomic profiling may be an approach to personalized medicine for these patients in the near future[25,186,187].

The addition of intensive plasmapheresis (used in a third of patients in the reviewed series[5,11,16-18,22,23]) along with MM or WM systemic therapy is an effective method for rapid decrease of cryoglobulins levels that has been reported to successfully improve the most severe cryoV manifestations, e.g., renal failure, and severe peripheral neuropathy[150,179]. On this basis, plasma exchange can be considered for severe life- or organ-threatening manifestations[188,189]. Plasma exchange has also been used to treat refractory manifestations such as non-healing skin ulcers[16-18,22,190,191], and is indicated before rituximab monotherapy in patients with WM with high IgM levels (> 4 g/dL), as this anti-CD20 monoclonal antibody is known to induce a paradoxical increase of IgM serum level and can worsen symptoms of hyperviscosity, neuropathy, or other cryoglobulinemic vasculitis symptoms[192-194].

Treatment of hyperviscosity syndrome

The hyperviscosity syndrome requires urgent plasma exchange to remove immune complexes and to rapidly reduce the concentration of serum cryoglobulins[189,195-199]. As plasmapheresis is considered a very effective but temporary approach that does not prevent the formation of new cryoglobulins, it should be used in conjunction with definitive cytoreductive therapy and other immunosuppressive agents[1,3,11,188,200]. A single session is able to reduce plasma viscosity by approximately 50%[200-202].

THERAPEUTIC MANAGEMENT OF NONVIRAL MIXED CRYOGLOBULINEMIC VASCULITIS

As in the case of type I cryoglobulinemia, treatment of patients with nonviral type II/III associated cryoglobulinemic vasculitis is based on the management of the underlying etiology (e.g., autoimmune or hematological disorder) in combination with nonetiological immunosuppressive therapy, adapted according to the extent of the severity of vasculitis [Figure 3][5,19,25,36,129,203]. In cases with essential mixed cryoglobulinemia, treatment is largely symptomatic[25].

Most treatment recommendations for non-HCV mixed cryoglobulinemia are derived from experience with HVC-related cryoV or have been adapted from effective therapy strategies employed in other small vessel vasculitides[3,121,204]. In this sense, mild vasculitis symptoms, such as limited purpura, constitutional symptoms, and arthralgias/arthritis, can be managed symptomatically or with low doses of corticosteroids

(alone or in combination with rituximab)[113,205]. As in other autoimmune diseases, long-term glucocorticoid administration is associated with frequent and sometimes severe adverse effects and comorbidities, and thus, short-term prednisone regimens are encouraged[25]. Intermittent relapses of isolated, nonulcerating cutaneous involvement can also be treated with non-steroidal anti-inflammatory analgesics, dapsone, or colchicine[206].

In the case of moderate and severe manifestations, e.g., peripheral neuropathy, glomerulonephritis, gastrointestinal vasculitis, digital ischemia or extensive necrotizing skin involvement, the combination of high-dose glucocorticoids (1 mg/kg/d prednisone) and rituximab (four weekly doses of 375 mg/m^2 or two 1-gr infusions separated by 2 weeks) is considered as the first line of treatment[3,19,121,130,207-225]. In patients with noninfectious mixed cryoglobulinemia, the administration of a combined regimen of rituximab and corticosteroids has been able to induce partial/complete clinical and immunological response in 64%-93% and 50%-81% of patients, respectively[5,9,10,35,121,207,220,222,224,226-229], and has demonstrated better clinical efficacy than corticosteroids in combination with conventional immunosuppressants[16,17,121,204]. Given the overall good efficacy of rituximab, with reported complete/partial remission higher than 70% in patients with severe manifestations such as peripheral neuropathy and membranoproliferative glomerulonephritis[5,25,135,207,220,224,225,230-232], and its demonstrated good safety profile[130,207,220,224,226,232], international expert societies now recommend this agent as the treatment of choice for patients with mixed cryoV suffering from moderate or severe manifestations[11,12,147,233,234].

Patients with life-threatening manifestations, for example, those with rapidly progressive kidney failure, alveolar hemorrhage, severe refractory cryoglobulinemic neuropathy, or diffuse involvement with heart or central nervous system manifestations, require urgent and intensive anti-inflammatory treatment to resolve acute organ damage in addition to the targeted therapy for the underlying etiology. For these presentations, treatment may include intravenous pulses of methylprednisolone, followed by oral high-dose systemic glucocorticoids in combination with rituximab and plasma exchange[1,5,9,12,15,25,146]. Plasmapheresis or immunoadsorption is considered a second-line therapy that may efficiently, rapidly, and temporarily reduce the burden of circulating cryoglobulins[25,189]. According to previous retrospective series, 10-14 sessions may induce improvement in 70%-80% of patients with peripheral neuropathy, rapidly progressive glomerulonephritis, or refractory skin ulcers[235,236]. Of note, the exchange used in plasmapheresis solution should be warmed to avoid cryoglobulin precipitation[3,237], and importantly, rituximab must be administered after plasma exchange to avoid its removal[236,238].

Although conventional immunosuppressive drugs have been largely replaced by rituximab, intravenous cyclophosphamide used in conjunction with corticosteroids remains a valid initial therapy in patients with organ- or life-threatening disease[1,5,9,25,130,146]. Methotrexate, mycophenolate mofetil, and azathioprine have been used to control mild to moderate disease manifestations in former series[239-241].

TREATMENT OF RITUXIMAB-RESISTANT MIXED CRYOGLOBULINEMIC VASCULITIS

Definition of rituximab-resistant disease

Although no standardized definition for rituximab-refractory cryoglobulinemic vasculitis exists, patients whose signs and symptoms are maintained or worsen within 4-6 weeks after treatment initiation, those with persistence of active clinical manifestations within 12 weeks after rituximab initiation, or cases with recurrence of active manifestations during rituximab treatment even after an initial response, have been categorized as non-responders in former publications[5,10,18,121,178,204,207,222]. For these patients, there is not a unanimously accepted therapeutic alternative [Figure 3].

In previous observational studies and small randomized clinical trials, the percentage of patients who do not respond to rituximab administration varied between 6%-17%[18,130,210,212,215,222,228,242-244], although this is still considered a rare event in clinical practice. In the French multicenter cryoV survey study, which analyzed data from 242 patients with noninfectious mixed cryoglobulinemia, 11% were considered resistant to first-line therapy with glucocorticoids plus rituximab[121]. In the same series, approximately 30% of patients with initial clinical response experienced an early relapse within the first year after induction therapy[121,229]. The characteristics of this particular subset of patients have been recently reported in the largest multicenter study on the management of nonviral mixed cryoV refractory to rituximab, which included 26 patients from 22 European countries[204]. According to this study, cryoV was primarily refractory to rituximab in 42% of cases, while the rest experienced an initial clinical response before suffering an early treatment failure[204].

When an individual presents with this clinical scenario, it is critical to reassess the patient's disease with the following objectives: (1) to evaluate treatment adherence and associated toxicity; (2) to rule out other systemic vasculitides or conditions that may mimic cryoV; (3) to identify chronic persistent damage or new underlying infectious-related comorbidities; and (4) to exclude progression of the hematological malignancy[5]. Furthermore, in addition to those cases that are truly refractory to rituximab or that became resistant to it due to the appearance of anti-chimeric antibodies, a small percentage of patients develop severe drug adverse effects that will prevent further use of the medication[226].

Treatment of refractory cryoglobulinemia vasculitis

In cases in which rituximab therapy fails to produce a clinical response or early relapses are observed, cyclophosphamide, biological agents (e.g., belimumab or tocilizumab), conventional immunosuppressive agents, plasma exchange, and other targeted therapies such as anti-plasma cell drugs (e.g., thalidomide, lenalidomide) are potential rescue approaches[15]. Unfortunately, none has been rigorously studied, and experience is based mostly on case reports and small series[121,204].

In the series of 26 rituximab-refractory patients, rituximab failure was attributed to active cutaneous, peripheral nerve, and kidney involvement in 72%, 56%, and 41% of analyzed cases[204]. Treatment regimens for these patients were heterogeneous and included glucocorticoids (92%), alkylating agents such as cyclophosphamide, chlorambucil, or bendamustine (43%), rituximab combined with other immunosuppressive agents (46%), plasma exchange (29%), belimumab (17%), conventional immunosuppressive drugs (mycophenolate mofetil, azathioprine, and methotrexate, 14%), other anti-CD20 monoclonal antibodies (4%), bortezomib (3%), and others (e.g., lenalidomide, ibrutinib, fludarabine, disulone, and tocilizumab)[204].

Cyclophosphamide (oral and intermittent intravenous pulses) has been used for several decades to effectively induce remission in severe ANCA-associated vasculitis. Similarly, in cryoglobulinemic vasculitis, previous series and uncontrolled case reports have shown that cyclophosphamide, in combination with high-dose glucocorticoids, was able to control organ- or life-threatening manifestations such as MPGN or severe peripheral neuropathy[130,188,195,245-248]. According to limited observational data[195,245,246], symptom improvement occurred in 75%-100% of cases with cutaneous or articular symptoms and in approximately 70% of those with kidney disease after cyclophosphamide administration. Further, in patients with cryoV resistant to rituximab, cyclophosphamide (and other alkylating agents) induced a clinical response in 82% of cases, although the immunological response was observed in only 30%[204]. Thus, cyclophosphamide may be considered a valid option for rituximab-refractory patients with acute flares and rapidly progressive cryoglobulinemic vasculitis[1,11,147,218,245-253]. The combination of cyclophosphamide or other alkylating agents with anti-CD20 therapy has also been reported, with estimated clinical efficacy higher to 70%[121,178,204].

With regards to biological therapies, the same study[204] also shows that the combination of rituximab plus belimumab provided the highest rates of clinical and immunological response (100% and 50%, respectively) in rituximab-resistant patients. This is in line with data from small series and clinical case reports suggesting that sequential administration of anti-CD20 treatment and belimumab is effective in patients with type II mixed cryoglobulinemic vasculitis refractory to (or relapsed after) rituximab monotherapy and other immunosuppressive drugs. In these publications, the addition of belimumab led to complete resolution or stabilization of moderate to severe refractory cutaneous, articular, peripheral nervous, and glomerular involvement[204,254-256]. The rationale for combining different B-cell targeting therapies that have already been tested in other autoimmune diseases stems from the B-cell proliferation and differentiation supported by the B-lymphocyte activating factor, which in turn results in increased immunoglobulin synthesis.

An interesting option includes the modulation or blockage of specific cytokines. For example, the anti-IL-6 receptor tocilizumab has been tried in a few patients with remarkable improvement in mild manifestations such as purpura, neuropathy, and myopathy[257]. In addition, in a previous pilot open-label study of patients with HCV-related vasculitis refractory to antivirals and/or rituximab, the administration of 4 cycles of subcutaneous low-dose IL-2 resulted in clinical improvement of skin, articular, and renal manifestations in 8 out of 10 cases[258]. Lastly, other potential therapies may include the use of bortezomib, new anti-CD20 monoclonal humanized antibodies such as obinutuzumab and ofatumumab, or the use of conventional immunosuppressive drugs (e.g., mycophenolate mofetil) in combination with long-term plasma exchange[15,204,240,259-262].

Although true refractoriness to rituximab is rare in patients with noninfectious mixed cryoV, the management of these patients is challenging as reported therapeutic strategies are only partially clinically and immunologically effective, and patients frequently relapsed[204]. Therefore, further studies are needed to identify new possible targets of therapy that may serve as rescue treatments for these patients.

Rituximab-associated immune complex vasculitis

Adverse events following rituximab administration have been reported in 15%-50% of patients with HCV or nonviral cryoglobulinemic vasculitis. Although most episodes are mild and transient, e.g., infusion-induced hypotension or allergic anaphylactoid reactions, 2% to 30% of cases develop severe adverse effects, e.g., infections, vasculitis "flares", myocardial infarction, thromboembolic events, hypo-gammaglobulinemia or late-onset neutropenia[207,222,223,228,243,263]. Serious infections, the most commonly observed severe complication, are associated with an elevated mortality, approximately of 50%. These are generally of bacterial origin, tend to affect the lower respiratory tract or the skin and soft tissues, and are observed more frequently in patients aged > 70 years, individuals with renal failure, and those treated with high glucocorticoid doses[121,207,222]. Rituximab has also been associated with fulminant disease in HIV and HBV active infections[264,265].

Vasculitis-like reaction following rituximab infusion is a phenomenon that has been reported in 3%-13% of patients with cryoV[207,222,226,266]. The immune complex vasculitis induced by rituximab refers to an organ- or life-threatening disease that presents with an acute episode of cutaneous involvement, renal failure, ischemic colitis, myocarditis, and/or severe nervous system manifestations within 2-4 weeks of rituximab administration[263,267]. In previous literature, these "flares" tend to develop more frequently after the first course of rituximab (75% of cases) and occur more frequently in patients with elevated levels of type II cryoglobulins (predominantly IgM *kappa*) and kidney vasculitis, cryocrit > 10% with very low C4 levels, those with B-cell lymphoma, and with the use of the so-called arthritis rheumatoid rituximab regimen (i.e., two 1-gr infusions separated by 2 weeks)[222,263,266,267]. The pathogenesis of this complication implicates massive tissue cryoprecipitation that results from an accelerated formation of immune complexes formed by

sera containing IgM *kappa*-mixed cryoglobulins with RFA and rituximab, an IgG1 *kappa*[263]. The formation of cryoprecipitating immune complexes has been confirmed *in vitro* and in kidney biopsies of patients with rituximab-associated vasculitis, where positive staining of rheumatoid factor IgM and IgG rituximab was identified in endomembranous deposits and vascular thrombi. Treatment of rituximab-associated vasculitis consists of high-dose glucocorticoids, plasma exchange, and intensive care support[263,267]. In severe cases, mortality is approximately 50% within the first 3 months after the vasculitis exacerbation episode[263,267]. Preventive measures may include the use of lower doses of rituximab or plasma exchange prior to rituximab administration in cases with elevated baseline levels of mixed cryoglobulins[222,267].

PROGNOSIS

CryoV may be associated with significant morbidity (e.g., chronic painful neuropathy, cardiovascular diseases, chronic kidney failure) and increased mortality[36,268]. The prognosis is influenced by factors such as age at disease onset, comorbidities, type and underlying etiology of cryoglobulinemia, severity of initial organ involvement, complications associated with vasculitis and treatment adverse effects, or development of B-cell malignancies[121]. For type I cryoglobulinemia, prognosis is particularly dependent on the underlying lymphoproliferative disorder.

The survival rate for type I cryoglobulinemia has been estimated at 97%, 94%, and 87% after the first, fifth, and tenth year of the disease, respectively[18]. The prognosis of patients with this type of cryoglobulinemia strongly depends on the presence of an underlying hematologic cancer, which is associated with a worse prognosis. The main causes of death include infections and the progression of hematologic malignancies[18]. With regard to noninfectious mixed cryoV, the overall survival rate after one, five, and ten years after diagnosis has been reported in 91%, 79%, and 65%, respectively[269]. Prognostic factors of poor outcome include age > 65 years and severe kidney, lung, or gastrointestinal involvement[113,121,269].

In the heterogeneous population of patients with mixed cryoV, observational studies have shown that sepsis is the leading cause of death in the short term (80% of cases). Uncontrolled vasculitis activity is the next most common cause of death, with the highest mortality rates associated with pulmonary hemorrhage, gastrointestinal ischemia, and CNS or heart involvement[5,14,20,35,36,118,121,270,271]. Cardiovascular complications, infections, and hematological malignancies are the most frequent causes of death after a prolonged disease course[272]. Of particular interest for the long-term outcome in these patients is the association between type II cryoglobulinemia and the development, 5 to 10 years after diagnosis, of secondary NHL (marginal zone lymphoma, diffuse large B-cell lymphoma, and lymphoplasmacytic lymphoma), which occur in approximately 5%-10% of cases[36,270,273-275]. Previous studies have shown that patients with noninfectious mixed cryoglobulinemia have a 4-fold increased risk of developing B-cell NHL[270], whereas this is 35 times higher than in the general population when type II cryoglobulinemia is associated with HCV[270,276]. In the latter, risk factors for the appearance of B-cell NHL include serum cryoglobulin levels > 0.6 g/L, development of cryoglobulinemic vasculitis, and hypogammaglobulinemia[277,278].

The prognosis of cryoV may also be impacted by disease flares, reported in 30%-50% of cases, which may be associated with increased morbidity and cumulative organ impairment[130,207,208,218,222,224,243,268]. Although the cause of the relapsing nature of nonviral cryoV is not known, data from HCV-related cryoV suggest that recurrences of disease activity may be related to the persistence of autonomous, pathogenic, cryoglobulinemic producing B-cell clones[279-281]. Previous studies have shown that cryoglobulins may still be detected in 20%-50% of non-viremic HCV-infected patients, and more importantly, relapses of vasculitis symptoms have been observed in 4%-11% of these patients in the presence of complete viral response[279-282]. Interestingly, although DAA are the treatment of choice for HCV-related cryoV, recent studies have

reported that, in comparison with IFN-based therapies, DAA may be associated with increased risk for HCV-independent relapses of cryoglobulinemic vasculitis, higher need of rescue therapy with rituximab, less efficient clearance of cryoglobulins, and lower decrease in the number of circulating pathogenic B cells[281,283-285].

This data suggests that people suffering from cryoV require a long-term follow-up with close and frequent monitoring for timely identification of disease flares, infectious complications, and cumulated organ damage associated with the disease or its treatment[3,25]. Frequent reassessments of the underlying disease, thereby allowing prompt identification of progression to overt hematologic cancer, should be regularly scheduled[3,129,207]. Prophylaxis against opportunistic infections (e.g., *Pneumocystis jiroveci*) and vaccinations according to age and immune status (e.g., influenza A, pneumococcus, varicella-zoster virus, and SARS-CoV-2) need to be administered[286,287].

CONCLUSIONS

Cryoglobulinemic vasculitis is a heterogeneous syndrome whose diagnosis and treatment represent a clinical challenge. Cryoglobulinemia is seen in the setting of systemic autoimmune diseases, hematological cancer, and infectious disorders. Management of cryoV is defined according to two major factors, that is, the severity of disease organ damage and the underlying associated etiology. In this sense, treatment of type I cryoglobulinemic disease should be focused on the underlying hemopathy, while patients with mixed cryoglobulinemic disease usually require a combination of rituximab and glucocorticoids. For those uncommon cases resistant to rituximab, the therapeutic management remains unclear and further investigation is needed to establish first-line treatment options.

DECLARATIONS

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All authors approved the final version of the paper.

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Consent for publication

The images presented were obtained with consent from patients.

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