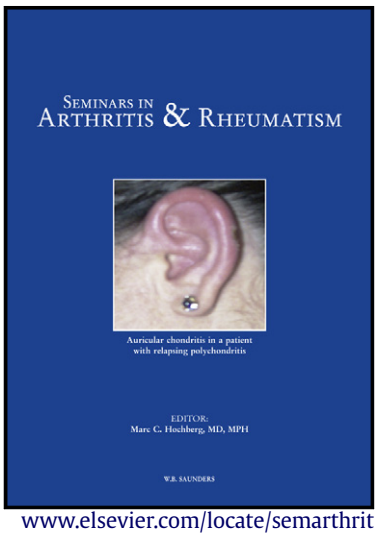

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Dilia Giuggioli MD, Andreina Manfredi MD, Federica Lumetti MD, Marco Sebastiani MD, Clodoveo Ferri MD

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REVISION

Cryoglobulinemic vasculitis and skin ulcers. Our therapeutic strategy and review of the literature.

Dilia Giuggioli, MD, Andreina Manfredi, MD, Federica Lumetti MD, Marco Sebastiani, MD, and Clodoveo Ferri, MD

Chair and Rheumatology Unit, University of Modena and Reggio Emilia, Medical School, *Azienda Ospedaliero-Universitaria, Policlinico di Modena, Modena, Italy.*

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Corresponding author:

Dr. Dilia Giuggioli, MD
Rheumatology Unit
Dpt of Internal Medicine
University of Modena and Reggio Emilia
Via del Pozzo, 71
41100 Modena Italy
Tel +39-059-4224053
Fax +39-059-4224178
E-mail: giuggioli.dilia@policlinico.mo.it

Abstract

Objective

Cryoglobulinemic vasculitis (CV) involving small- and medium-sized vessels is very frequently associated to hepatitis C virus and may be responsible for multiple organ involvement, including skin ulcers (SU). These latter are often non-healing cutaneous lesions, possibly complicated by local infection and gangrene; they may severely affect the patients' quality of life and the overall prognosis. Therefore, the treatment of cryoglobulinemic SU is particularly challenging in the clinical practice.

The present work evaluated the prevalence and correlations of cryoglobulinemic SU with other clinico-epidemiological features of CV; moreover, our long-term experience with the management strategies of these cutaneous lesions was compared with the world literature on this topic.

Methods

The study included 126 CV patients (24 M and 102 F, age 69±11.2SD years, disease duration 7±6.9SD years), followed at our Rheumatology Unit during the last decade. All patients were carefully evaluated as regards the entire cryoglobulinemic syndrome with particular concern for clinical characteristics and treatment of SU.

Results

Among 126 CV patients 36 individuals (29%) experienced at least one episode of SU, more commonly localized at the lower limbs. Patients with complicating SU showed significantly higher percentage of purpuric manifestations ($p < 0.01$), liver ($p < 0.001$), peripheral nerve ($p < 0.02$), and/or thyroid involvement (p 0.019).

Therapeutic approach to SU included both systemic (immunosuppressors, corticosteroids, and/or plasma exchange) and local treatments. These latter consisted of sharp or surgical debridement as well as interactive dressing according to the condition of wound bed, perilesional skin, and the possible presence of infection, detected in 29/36 (81%) of individuals. Al patients underwent to analgesic treatment for SU-related background pain as well as procedural pain, which was critical for an effective local SU management.

The large majority of SU healed in a variable time interval according to severity of the single lesion; only 5 patients with very severe, non-healing SU needed amputation.

The updated review of the literature revealed the presence of SU in around a quarter of CV patients. Among systemic treatments, the anti-CD20 monoclonal antibody, rituximab, represents one of the most effective and frequently employed therapies; while available data focusing on local therapeutic approach are generally limited to anecdotal observations.

Conclusions

On the whole, the treatment of cryoglobulinemic SU should be tailored on the single patient's conditions using combined systemic and local treatments; lesional sharp debridement and interactive dressing as well as procedural pain management were decisive, particularly for more severe, non-healing cutaneous lesions.

Introduction

Mixed cryoglobulinemia syndrome (MCs) is a systemic vasculitis characterized by multiple organ involvement due to the vascular deposition of immune-complexes, mainly the cryoglobulins (1-7). The term cryoglobulinemic vasculitis (CV) is frequently used as synonym. B-lymphocyte expansion represents the underlying pathological alteration frequently triggered by hepatitis C virus (HCV) infection (6-9).

Leukocytoclastic vasculitis is the histopathological hallmark of CV; it may involve small- and medium-sized vessels and may be responsible for multiple organ involvement (1-7). According to its first description as autonomous disorder (1), MCs is characterized clinically by a triad - purpura, weakness, arthralgias- and by a series of pathological conditions, including chronic hepatitis, membranoproliferative glomerulonephritis (MPGN), peripheral neuropathy, skin ulcers, diffuse vasculitis, and, less frequently, by lymphatic and hepatic malignancies (1-8). The presenting symptoms largely vary among MCs patients; at the initial observation, they show different clinico-serological patterns, varying from apparently isolated serum mixed cryoglobulins to complete cryoglobulinemic syndrome.

The skin lesions, in particular the orthostatic purpura, represent the most frequent manifestations that may appear at any time during the clinical course of MCs (1-7). Purpuric manifestations are generally intermittent, while their dimension and diffusion largely varied, from sporadic isolated petechias to severe vasculitic lesions, often complicated by torpid skin ulcers (SU), generally localized to lower and/or upper limbs, including distal necrosis of hands and feet. (Fig 1). They are the direct consequence of vasculitic alterations with the possible contributions of various co-factors, in particular chronic venous insufficiency, physical stress, mainly the prolonged standing, and/or muggy weather (5-7). In addition, the contribution of hemorheological disturbances due to high cryocrit levels may also be taken in account.

The treatment of cryoglobulinemic SU is particularly challenging. Cutaneous manifestations are prevalent in the lower limbs, where the above-mentioned pathogenetic co-factors may be concurrent, more often in patients receiving long-term steroid treatment; but they may also affect other cutaneous areas of the extremities such as fingers and toes (6, 7). SU are painful, non-healing, and often complicated by local infection; moreover, they may severely affect the patients' quality of life. Systemic treatments of MCs with/without SU, directed at improving the immune-system alterations of and/or HCV eradication, are largely reported in the world literature (5-16); while, specific therapeutic strategies of cryoglobulinemic SU, particularly with regards to local treatments that can be decisive for the most severe lesions, are poorly addressed (5-16).

The present study focused on the clinico-epidemiologic characteristics and management strategies of cryoglobulinemic SU in a large series of MCs patients followed at our Rheumatology Unit. In addition, the observed findings were compared to those emerging from the updated review of the literature on this topic.

Patients and Methods

The study evaluated 126 patients with CV (24 M and 102 F, age 69±11.2SD years, disease duration 7±6.9SD years), followed at our Rheumatology Unit during the last decade and classified according to the current criteria (5, 6, 17). Demographic and clinico-serological features of all MCs patients were evaluated according to previously reported methods (5 ,6; Tab.1). According to their localization, SU comprise two main types of lesions, namely distal necrotic wounds of the digits and toes and cutaneous ulcers of lower limbs (Fig. 1a: orthostatic purpura, b: digital U, c: SU of lower limbs, d: SU of toes). The evaluation of SU included the

number, size, and depth of lesions, wound-bed conditions, presence of granulation tissue, exudates, necrosis, and/or infection (18, 19). In the presence of perilesional erythema, swelling, abundant purulent exudates, and/or distinctive odor, suggesting possible bacterial infection, microbiological examinations were also performed by means of wound swabs. In addition, patient self-evaluation of SU-related pain was performed using a visual analogue scale (VAS, range 0-10). In all cases the therapeutic strategy included systemic and local treatments tailored to individual clinical status (6-16). Systemic treatments were decided according to the severity/activity of the whole MCs, including SU and possible comorbidities, and generally based on combined corticosteroids (CS), cyclophosphamide (CPX), low antigen-content diet (LAC-diet), rituximab (RTX), and/or antivirals (6-16; Fig. 2, 3). Finally, the treatment of SU-related chronic pain and procedural pain was necessary in all cases in order to improve the patients quality of life as well as their compliance to local wound care (Fig. 3; 20).

Local treatment was regularly performed according to wound bed preparation of the European Wound Management Association and the World Union of Wound Healing Societies' consensus statements (18, 19). The wound bed preparation is summarized in the acronymous TIME (18, 19), which usefully recall to the most important aspects of ulcer evaluation and management: necrotic tissue, infection/inflammation, moisture balance, epitelization (Fig. 3). To obtain the best results from wound bed preparation, we used active dressing; these medications actively interact with the wound tissues in developing of cellular matrix and promoting the entire healing process. Among the huge number of available active medications, their use was defined in the course of wound management according to careful clinical evaluation of the single lesion. The most used products in our experience were the alginate (non-woven absorbent fiber derived from different types of algae and seaweeds), hydrocolloid (wafer type of self-adhering dressing containing gel-forming agents in an adhesive compound laminated onto a flexible, water-resistant outer layer), hydrofiber (soft, sterile, non-woven pad or ribbon dressing composed of sodium carboxymethylcellulose), hydrogel (water based-gel wafer able to promote moist environment and removal of necrotic tissue through autolytic debridement), and polyurethane foam or film (open-cell hydrophilic polyurethane foam sheets, permeable to gas and water vapor, with an hydrophobic surface).

The CV-related SU refractory to conventional therapies were usefully treated by means of growth factors as the homologous platelet gel (21, 22). Finally, for more severe and hard-to-heal skin lesions, skin grafting, skin bank bioproducts, especially cyropreserved skin and de-epidermized dermis (DED) and/or others skin substitutes were used (23). Since SU complicating CV are extremely painful, adequate pain control was carried out (24-29). In all 36 CV patients with skin wounds a long-lasting analgesic treatment for chronic pain, usually defined as background pain, was done by means of opioids (oral oxycodone) and pregabalin. The procedural pain was treated with topical application of lidocaine/prilocaine cream (EMLA) for skin ulcers with mild pain (VAS <5), while the addition of local ± oral morphine was necessary to treat the more severe lesions (VAS >5) (29). In all cases, a team of operators with specific experience carried out such integrated therapeutic approach.

Review of the literature. A PubMed search up to March 2014, with the key words 'cryoglobulinemic skin ulcers', 'cryoglobulinemic vasculitis', 'mixed cryoglobulinemia', 'mixed cryoglobulinaemia', 'cryoglobulinemic skin involvement', and 'skin ulcer treatment' was done at PubMed, Scopus, Thomson Reuters' Web of Science, EMBASE, Asian Science Citation Index (ASCI), and IndMed.

to find published clinical studies and case reports regarding patients with CV complicated by SU.

Results.
Clinico-serological features of our MCs patients with/without SU are shown in Tab. 1. Out of 126 MCs patients 36 individuals (29%) experienced at least one episode of SU localized at the lower limbs; in addition, 9/36 (25%) patients developed at least one episodes of digital SU (Tab. 2). Recurrent episodes characterized by one or multiple skin lesions were observed in the majority of individuals (31/36, 86%). Skin lesions were more frequently found in males (38%) than in females (26%).
Moreover, one or more episodes of infected SU were observed in 29/36 (81%); the involved infectious agents were S. Aureus in 55% of cases, P. Aeruginosa and Enterobacter in 24 and 21%, respectively. The 36 MCs patients with complicating SU revealed some interesting peculiarities if compared to MCs patients without (Tab. 1); in particular, they showed a significantly higher percentage of purpuric manifestations ($p < 0.01$), liver ($p < 0.001$), peripheral nerve ($p < 0.02$), and/or thyroid involvement (p 0.019).
In all 36 patient**s** with cryoglobulinemic SU the therapeutic strategy was based on combined systemic and local therapies, including pain treatment (Tab. 2; Fig. 2, 3).

Systemic treatment. Systemic treatment in patients with SU was decided according to same therapeutic strategies usually followed for the whole MCs with some specific modifications (Fig. 2, 3). The treatment of MCs may be carried out at three different levels: a) the etiological treatment of HCV-associated MCs is directed at the eradication of chronic HCV infection; b) the pathogenetic therapies, able to reduce the autoimmune-lymphoproliferative alterations, mainly B-lymphocyte expansion and autoantibodies production; and c) pathogenetic/symptomatic therapies in order to improve the tissue lesions due to immune-complex-mediated cryoglobulinemic vasculitis (5-16; Fig. 2). Tab. 2 reports the different therapies employed in our 36 cryoglobulinemic patients with SU, in all cases as combined treatment tailored to the single patient on the basis of the activity/severity of MCs and comorbidities. Furthermore, in 29 patients developing one or more episodes of infected SU systemic antibiotic regimens were necessary.

Local therapy. Local therapy of single SU was invariably performed according to the wound bed preparation procedures (19, 20; Fig. 3). Each lesion was preliminarily treated with topical anesthetic EMLA to reduce the procedural pain; moreover, in patients with pain VAS >5 the use of both local and systemic morphine was necessary (29). Sharp or surgical debridement was performed in all cases; while interactive dressing was decided after a careful evaluation of the condition of wound bed, perilesional skin, and the possible presence of infection. In some cases (22%) a sensibilization reaction to dressing medications with erythema and itch in perilesional skin were observed.
Among 36 patients with SU 18 individuals developed a very severe episode of SU of the lower limbs unresponsive to the above-described systemic and local treatments. Therefore, in 14/18 SU dermal equivalent or autologous skin grafting were used as adjunctive therapy to conventional local treatment; namely, 12/14 SU were treated with composite grafts from skin bank consisting of DED, followed by complete resolution of the lesions in 5 and a marked improvement in others 3; while 4 lesions showed an initial improvement complicated by local infection requiring multiple skin implants and prolonged antibiotic therapy. In 2/14 with wider SU autologous skin grafting was able to improve the skin wounds.
Finally, in the other 4/18 non-healing SU an attempt with local homologous platelet gel was decided, followed by complete healing in one case and a marked improvement in two, while the fourth lesion was complicated by severe infection (P. Aeruginosa), requiring long-term systemic antibiotic therapy.

Analgesic treatment. Patients with skin lesions were invariably treated with analgesics for background pain (Fig. 3); according to patient's pain VAS, referred to the most painful lesion in the presence of multiple lesions. In the presence of mild pain VAS (≤4) the SU was usefully treated with paracetamol (1g x 2/day) or tramadol (150mg/day), while for moderate-severe pain VAS (>4) scores combined treatment with opioids (oral oxycodone, medially 20mg/day,) and pregabalin (medially 300mg/day) was necessary. Finally, SU associated to severe pain scores (VAS 9-10/10) required adjunctive oral morphine (5mg/day sublingual morphine sulphate, Oramorph).

Before each session of local management, lesions were invariably treated with the application of EMLA as above mentioned; a good compliance during the entire session of debridement and dressing was observed mainly in patients with cutaneous lesions characterized by mild pain VAS at baseline. While, procedural management of SU in patients with pain VAS >4 needed a combined therapy of EMLA and local morphine, or both local and oral morphine, according to the previously described timing of procedural pain management (29). In only two individuals with particularly severe SU, complicated by infection and gangrene, procedural analgesic treatment needed to be integrated with IV morphine (29).

In all instances, analgesic treatments of background and procedural pain revealed manageable and well tolerated, in no cases sensitization phenomena were observed.

On the whole, the majority of SU healed, even if the positive outcome was obtained in a variable time interval according to the severity of the single lesion and after one or more attempts of combined therapies. Generally, the healing of small and superficial wounds was followed by complete re-epithelialization, while the healing of particularly severe SU lead to more or less extensive skin scar. Only five patients with very large lesions of the lower limbs, complicated by gangrene and local infection, needed surgery at different levels: in two cases through-the-knees amputation, distal of ankle in one, and single toe amputation in the other two.

Review of the literature. As regards the prevalence of SU in MCs patients, available data are limited to 11 clinical reports published in the world literature, often characterized by relatively small patients series with frequent contrasting findings (Tab. 3). In these cohort studies (2-4, 7, 8, 30-35), the reported prevalence of SU ranged widely, from 4.7 to 30% of MCs patients. In our large series of 231 patients observed for a long-term follow-up period (7) this complication affected a significant proportion of individuals (22%).

Similarly, data regarding the therapeutic approach to SU complicating CV included 46 studies (11, 14, 16, 36-78, Tab. 4); only 13 reports regards to CV patients' series (11, 14, 16, 36-45), while the majority (no. 33) describes anecdotal observations of single cases (28/33) or very small series of 2-5 patients (5/33). The patients' clinico-epidemiological and virological features are not available in all reports; these patients' series were characterized by serum type II mixed cryoglobulins and HCV seropositivity in the majority of cases (Tab. 4). Considering the 13 cohort studies (11, 14, 16, 36-45), the prevalence of SU widely ranged from 12.5 to 50%, it was medially higher compared to the cohort studies reported in Tab. 3. This discrepancy may reflect a selection bias due to the recruitment for therapeutic trials of patients with more severe MCs, including the SU. The first 13 studies (Tab. 4) were generally carried out during the last decade. The employed systemic treatments are largely variable; however, the use of rituximab, alone or in combination with antivirals represents the most frequent therapeutic approach, i.e. 12/13 studies. Almost invariably they were retrospective studies reporting the effect of systemic treatments in patients consecutively enrolled in single referral centers or as multicenter study in one case (11). In only one controlled trial a higher prevalence of SU healing was observed in the group of patients treated with rituximab compared to those

treated with other therapies (45). Of note, the local treatments were never mentioned in these cohort studies (11, 14, 16, 36-45). Similarly, only 10/28 anecdotal observations (49, 51, 55, 60, 62, 64, 66, 67, 70, and 78) reported local treatments of SU, more often without detailed information. With regards the outcome of SU, the employed treatments were generally followed by the healing of cutaneous lesions, while amputation was observed in only one case.

Discussion

The present study firstly focused on one of the most challenging complications of cryoglobulinemic vasculitis by reporting our long-term experience in the management of SU in patients with MCs, as well as by analyzing the world literature on this topic.

In a large series of MCs patients enrolled at our rheumatology unit during the last decade one or more episodes of SU were recorded in almost one third of individuals, more frequently in males; the large majority of patients developed recurrent, difficult to heal, and often multiple skin lesions. These complications were significantly more frequent in patients with clinically severe purpuric manifestations, liver, peripheral nerve, and/or thyroid involvement, as well as in the serological subset of type II mixed cryoglobulinemia. On the whole, the association of recurrent SU with other important clinical symptoms seems to characterize a more aggressive clinical variant of CV. The majority of SU were localized to lower limbs and frequently complicated by local infections; both conditions may make more difficult the management of cutaneous lesions, which *per se* are scarcely responsive to various treatments. Following the experience of other specialties regarding the treatment of non-healing SU such as diabetes-associated manifestations (18-21), we tried to develop during the years a holistic therapeutic strategy to cryoglobulinemic SU. It was based on the careful patient's assessment of the whole MCs (6, 7, 11), as well as of local characteristics of the single skin lesion, and the presence of systemic and local comorbidities (diabetes, other endocrine, metabolic, peripheral artero-venous involvement, and/or infections, etc.). In all instances, systemic treatment was tailored on the single patient using antiviral and/or pathogenetic-symptomatic therapies (6-17); these latter were employed, generally as multiple drug therapy, namely, immunosuppressors, steroids, and/or plasma exchange (6-17). Among pathogenetic treatments the use of anti-CD20 monoclonal antibody, rituximab, alone or as combined/sequential treatment, can be regarded as the most useful and manageable drug (10-17). In all cases of CV complicated by SU the combination of systemic and local treatments was necessary; rather, our experience suggested that in patients with more severe, resistant lesions the intensive local therapeutic approach may be decisive to the healing of the lesions, or at least to avoid or to limit the most dangerous consequences of SU such as gangrene and amputation. Local treatment was mainly based on the standard procedures of wound bed preparation that permit the sharp or surgical debridement (18-29); this latter are critical for the overall outcome of the lesions. The removal of necrotic and devitalized tissue, slough and fibrin from the ulcer limits the risk of infections and promotes the growth of granulation tissue that is essential for the healing process (18-29). The interactive dressing may comprise different medications, including the use of dermal equivalent or autologous skin grafting in the largest lesions, and/or homologous platelet gel in SU particularly difficult to treat. The use of homologous platelet gel in the treatment of CV-related SU revealed useful to obtain a rapid growth of granulation tissue and progress of the wound edge (21, 22). In all cases, a careful evaluation, including microbiological swab analysis, of possible infectious complications was carried out in order to decide the correct systemic antibiotic therapy. Even if healing represents the major purpose of treatment, the management of cryoglobulinemic SU-related pain has been identified as a major issue (25-29); a valuable analgesic treatment was employed in all cases according to both patients' pain VAS and objective difficulties of the single lesion. Analgesic therapies were mainly directed to improve the SU-related *background* pain as well as the procedural pain (29). The first one can be

particularly difficult to control in those patients with concomitant neuropathic pain due to the peripheral neuropathy that frequently complicated the MCs (6, 7); while the management of procedural pain was critical in order to permit a valuable wound bed preparation, specially the debridement and dressing of the lesion (29).

The analysis of the world literature on these challenging complications of MCs revealed a limited number of clinical studies reporting the prevalence of SU (2-4, 7, 8, 30-35). Among available clinical cohort studies, often relatively small patients series, data on the prevalence of SU in MCs are generally contrasting; the reported prevalence ranged from 4.7 to 30% of cryoglobulinemic patients (2-4, 7, 8, 30-35). The largest patients series with longer follow-up period (7) showed the presence of SU in a significant proportion of individuals, suggesting that this complication may affect at least a quarter of patients.

Data regarding the treatment of cryoglobulinemic SU are generally scarce, particularly as regards the description of specific local treatments (11, 14, 16, 36-45). In both cohort studies and anecdotal reports, the treatment of SU is frequently cited in the context of the therapeutic approach to the whole MCs.

The etiopathogenesis of SU may recognize the same process involved for other clinical manifestations of the MCs (5-9). Firstly, the immune-complex mediated leukocytoclastic vasculitis involving small vessels, i.e. arterioles, capillaries, and venules, is the main pathological alteration responsible for vascular injury and consequent ischemic lesions (5-9). Moreover, a number of other co-factors may contribute to the development SU, namely the macrovascular involvement, more often the venous chronic failure of the lower limbs, the long-term steroid treatment with metabolic and cutaneous alterations, and other factors such as long-standing posture and/or muggy weather (6, 7). In our five patients with severe SU needing amputation the above co-factors were particularly evident, mainly the presence of large-medium sized arteriopathy. Only one comparable case is reported in the literature (67).

The treatment of MCs is particularly complex due the coexistence of infectious, autoimmune, and lymphoproliferative alterations (6-17). This multifaceted disorder is characterized by unpredictable clinical course, characterized by alternating periods of disease remission or scarce activity and sudden exacerbation or possible neoplastic complications (6-7). In this context the appearance of SU, often resistant to systemic treatments, may further complicate the therapeutic approach and severely affect the patient's quality of life. Therefore, local treatment of cryoglobulinemic SU with advanced wound management algorithm may optimize the overall therapeutic approach of MCs.

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Legend to the Figures

Fig. 1

Cryoglobulinemic vasculitis (CV) complicated by different skin manifestations:

a) orthostatic purpura secondary to necrotizing leukocytoclastic vasculitis of the skin;

b) symmetrical hyperpigmentation of the skin on the legs after repeated episodes of purpura; both orthostatic purpura and these permanent ochraceous lesions represent the typical skin manifestations of CV;

c) more severe vasculitic manifestations showing multiple skin ulcers with the presence of central necrotic tissue and slough (adherent fibrous material derived from proteins, fibrin and fibrinogen) in the wound bed. The presence of devitalized tissue acts as a physical barrier to epidermal cell migration and healing process; the borders of skin ulcers are irregular and scarcely reactive.

d) superficial cutaneous lesions coexist with a severe skin ulcer extremely painful. The necrotic tissue appears as a moist, yellow area with central dry black scar. Reddish and swollen borders, representing the first sign of skin tissue destruction, surround the wound until metatarsophalangeal skin areas.

e) distal gangrene of the third finger of the right hand is associated with infected area under the necrotic tissue. The progression of the gangrene was treated with aggressive combined therapy leading to complete resolution of the vasculitic lesion.

f) confluent severe non-healing skin lesions were ultimately complicated by gangrene of the distal foot. A red line on the skin delimiting the necrotic tissue characterized the areas of gangrene. It became progressively dark, while the presence of both necrotic tissue and fibrin under the gangrene contributed to local infection. Combined systemic and local treatments did not affect the progression of these severe skin lesions needing below-the ankle amputation.

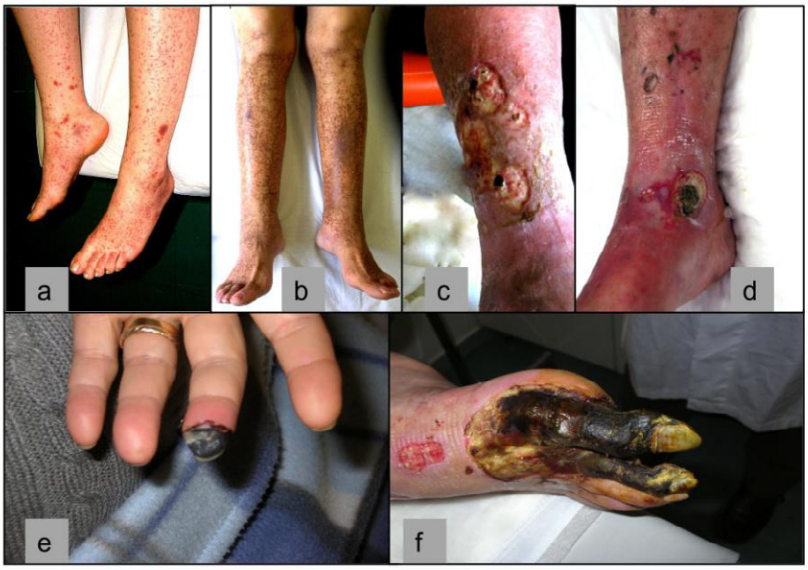


Fig. 2

The therapeutic strategies to mixed cryoglobulinemic syndrome (MCs) or cryoglobulinemic vasculitis should be decided on the basis of the etiopathogenetic cascade that leads from hepatitis C virus (HCV) infection to multiple immune-system alterations, mainly the B-cell proliferation, and lastly to autoimmune manifestations such as small vessel cryoglobulinemic vasculitis secondary to vessel deposition of circulating immune-complex (CIC), mainly mixed cryoglobulins. This latter may be complicated by malignancies, mainly B-cell lymphoma. In this scenario, MCs can be treated at 3 different levels by means of etiological, pathogenetic, and symptomatic therapies. The antiviral therapy aims to eradicate the HCV; it represents the etiological treatment of patients with HCV-associated MCs. The anti-CD20 monoclonal antibody (rituximab) can be considered the most useful and safe pathogenetic treatment of cryoglobulinemic vasculitis. In selected patients with active clinical manifestations the sequential or combined therapy with antivirals and rituximab can be usefully employed. Cycles of low-dosage corticosteroids may be sufficient in patients with mild manifestations such as arthralgias and/or purpura; on the contrary, very severe, rapidly progressive complications (glomerulonephritis, sensory-motor peripheral neuropathy, non-healing skin ulcers with gangrene, and/or widespread vasculitis) combined therapy with immunosuppressors, corticosteroids, and plasma exchange is necessary (see also text).

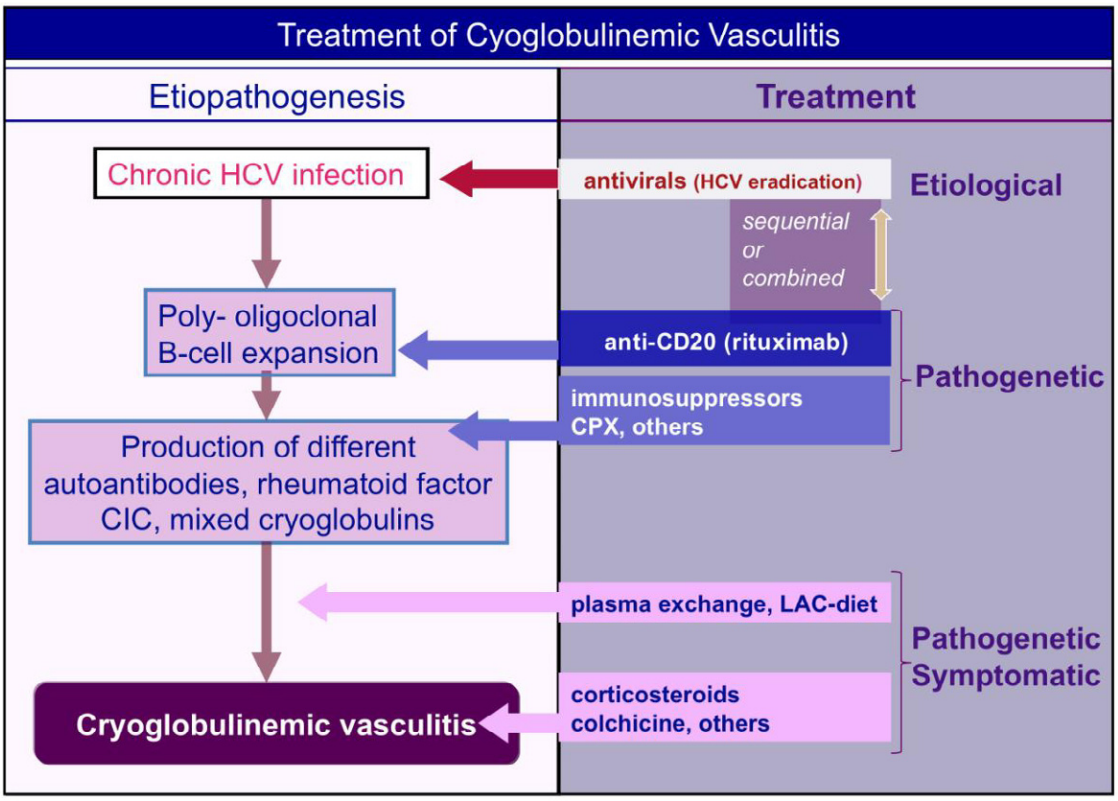
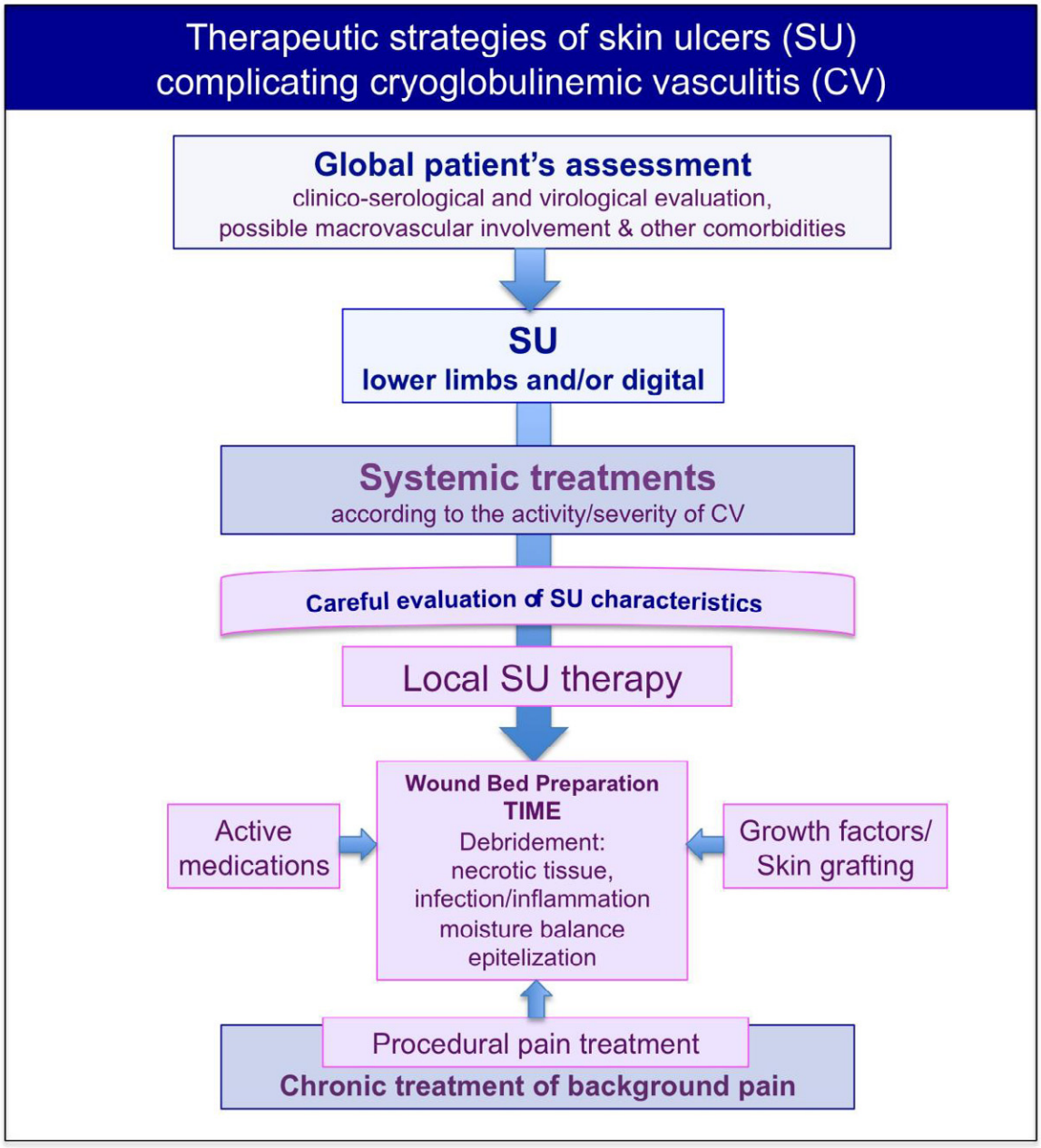


Fig. 3.
The figure summarizes the therapeutic strategies in patients with cryoglobulinemic SU followed at our Rheumatology Unit. In all cases a thorough clinico-serological patient's assessment, including the frequent comorbidities, is mandatory. In patients with SU of the lower limbs the possible contribution of macrovascular involvement should be also investigated. Systemic treatment (see fig. 2) must be decided according to activity/severity of the whole MCs; in all cases both systemic and local treatments should be tailored on the single patient's conditions. Local management of the SU is based on the careful evaluation of the single lesion characteristics: size, depth, wound-bed conditions, and presence of granulation tissue, exudates, necrosis, and/or infection. Therefore, an accurate sharp and/or surgical debridement represents the most important step of SU local management, with the supportive use of active medications and in the more severe cases of growth factors and/or skin grafting. Besides the treatment of chronic background pain, local management of SU requires the use of analgesic drugs in order to control the procedural pain. This latter is crucial to obtain an effective SU debridement, which in the presence of very severe lesions may require additional systemic analgesic therapy (see text).


Therapeutic strategies of skin ulcers (SU) complicating cryoglobulinemic vasculitis (CV)
Global patient's assessment
clinico-serological and virological evaluation, possible macrovascular involvement & other comorbidities
SU
lower limbs and/or digital
Systemic treatments
according to the activity/severity of CV
Careful evaluation of SU characteristics
Local SU therapy
Active medications
Wound Bed Preparation
TIME
Debridement: necrotic tissue, infection/inflammation
moisture balance
epitelization
Growth factors/ Skin grafting
Procedural pain treatment
Chronic treatment of background pain

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Tab. 1.

Demographic and clinico-serological fetaures of our 126 MCs patients		
		%
Patients no	126	
M/F	24/102	
Mean age (years ±DS)	69±11,2	
Disease duration (years ±DS)	7±6,9	
HCV associated MC	115/126	91.26%
Cryoglobulin characterization		
Type II	88/126	70%
Type III	26/126	20.63%
Clinical manifestations		
chronic hepatitis	69/126	54.76%
purpura	96/126	76.19%
weakness		
arthralgias		
vasculitic skin ulcers	36/126	28.57%
renal involvement	24/126	1904.00%
peripheral neuropathy	85/126	6746.00%
B cell NHL	16/122	12.69

Tab. 2. Clinical fetaures and treatments of 36 MCs patients with vasculitic skin ulcers.

	no.	%
Skin ulcers localization		
lower limbs (legs and/or feet)	36/36	100
lower limbs+digital ulcers	9/36	25
Infection*	29/36	81
Systemic treatment°		
IFN+RIBA	8/36	22
RTX	20/36	55.5
CPX	8/36	22.2
PE	15/36	41.6
Steroids	36/36	100
low-antigen diet	36/36	100
Antibiotics	29/36	81
Analgesics	36/36	100
Combined treatments	36/36	100
Local treatment	36/36	100

MCs: mixed cryoglobulienmic syndrome (cryoglobulinemic vasculitis)
*observed at least one time during the patient's follow-up
°employed, alone or as combined therapy, at least one time during the patient's follow-up
IFN+RIBA: alpha-interferon plus ribavirin;

Tab. 3. Prevalence of vasculitic SU in patients with MCs: review of the lit

	MCs	SU
Author, year (ref)	**Pts no.**	**%**
Brouet JC, 1974 (2)	65	6.2*
Gorevic P.D, 1980 (3)	35	28.6°
	40	30°°
Invernizzi F , 1983 (4)	79	10
Cohen SJ, 1991 (30)	47	21
Ferri C, 2004 (7)	231	22
Casato M, 2008 (31)	64	30
Landau DA, 2010 (32)	85	4.7
Dammacco F , 2001 (8)	200	30
Perniola R, 1999 (33)	88	8
Foessel L, 2011 (34)	33	21.2
Liou Y.T 2013 (35)	96	18.8
Range	33-231	4.7-30

MCs: mixed cryoglobulinemia syndrome; SU: skin ulcers; *4.4% leg ulcers plus 1.8% defined as distal necro
°mean prevalence reported in previous literature since 1965; °°referred to personal pts series

Tab. 4. Treatment of MCs complicated by vasculitic skin ulcers (SU): review of the literatur

Author, year (ref)	MCs pts no.	MCs HCV+	MCs type II/III	SU no. (%)	Treatments		outcome of SU
					Systemic	local	H/U/W
Cohort studies							
Rieu V, 2002 (36)	40*	33	24/16	20 (40.8%)*	IFN, PE, CPX, AZA, CS	nd	25/nd/nd
Auzerie V, 2003 (37)	7	5	7 / 0	7 (46.6%)	CPX, PE**	nd	15 / 0 / 0
Zaja F, 2003 (38)	15	12	15 / 0	5 (33.3%)	RTX	nd	5 / 0 / 0
Sansonno D, 2003 (39)	20	20	13 / 7	7 (35%)	RTX	nd	3 / 2/ 2
De Vita S, 2007 (40)	28	nd	28 / 0	8 (28.5%)	RTX	nd	5 / nd / nd
Visentini M, 2007 (41)	6	6	6 / 0	3 (50%)	RTX	nd	2 / 0 / 1
Roccatello D, 2008 (42)	12	11	12 / 0	3 (25%)	RTX	nd	3 / 0 / 0
Saadoun D, 2008 (14)	16	16	14, / 2	2 (12.5%)	RTX plus IFN-RIBA	nd	2 / 0 / 0
Petrarca A, 2010 (43)	19	19	17 / 2	3 (15.7%)	RTX	nd	3 / 0 / 0
Dammacco F, 2010 (16)	22	22	20 / 2	5 (22.7%)	RTX plus IFN-RIBA	nd	4 / 0/ / 1
Visentini M, 2011 (44)	27	27	27 / 0	9 (33.3%)	RTX	nd	6 / nd / nd
Ferri C, 2011 (11)	87	80	73/14	24 (28%)	RTX	nd	15 / 2 / 7
De Vita S, 2012 (45)	57	53	57 / 0	7 (12.3%)	RTX (5); non-RTX (2)°	nd	6 / 1 / 0
Case reports							
Butler J.D, 1963 (46)	1	nd	nd	1	chloroquine	nd	0 / 1 / 0
Fontaine J.L, 1970 (47)	1	nd	nd	1	nd	nd	0 / 0 / 1
Riu R, 1970 (48)	1	nd	nd	1	nd	nd	nd
Goldschmidt-Clermont JP, 1978 (49)	1	nd	nd	1	none	graft**	1 / 0 / 0
Geltner D, 1981 (50)	5	nd	nd	3	combined therapies^	nd	3 / 0 / 0
Delaney V.B, 1984 (51)	1	nd	1 / 0	1	PE	yes	1 / 0 / 0
Ralston S.H, 1988 (52)	1	nd	nd	1	nd	nd	nd
Sundar U, 1994 (53)	1	nd	1 / 0	1	nd	nd	nd
Cheung N.T, 1995 (54)	3	nd	nd	3	IFN 2α	nd	3 / 0 / 0
McGovern T.W, 1996 (55)	1	0	1 / 0	1	PE	yes	1 / 0 / 0
Machet L, 1997 (56)	1	nd	1 / 0	1	PE+ AZA+CS	nd	0 / 0 / 1
Konischi M, 1997 (57)	1	0	1 / 0	1	CS	nd	1 / 0 / 0
Wisnieski JJ, 1998 (58)	1	1	1 / 0	1	IFNα2B + CPX+CS	nd	0 / 0 / 1
Cavanna L, 2000 (59)	3	3	1 / 0	3	rhGM-CSF	nd	3 / 0 / 0
Mahabir R.C, 2001 (60)	1	1	1 / 0	1	PE, IFNα2B, IV Ig	graft	0 / 1 / 0
Ghijsels E, 2004 (61)	1	0	1 / 0	1	RTX	nd	1 / 0 / 0
Ghobrial IM, 2004 (62)	1	0	1 / 0	1	RTX	yes	1 / 0 / 0
Cakir O, 2005 (63)	1	0	0 / 1	1	CPX	nd	1 / 0 / 0
Suárez-Amor O, 2006 (64)	4	0	2, / 2	3	CS	yes	3 / 0 / 0
Hamaguchi M, 2007 (65)	1	0	1 / 0	1	Mizoribine + CS	nd	1 / 0 / 0
Brownell I, 2007 (66)	1	1	0 / 1	1	none	yes	1 / 0 / 0
Mironiuc A, 2008 (67)	1	1	nd	1	CS+ CPX + INFα	surgery	amputated
Braun A, 2008 (68)	1	0	0 / 1	1	RTX	nd	1 / 0 / 0
Tallarita T, 2009 (69)	1	1	1 / 0	1	RTX+ CS + PE	nd	1 / 0 / 0
Mulder G, 2009 (70)	1	nd	nd	1	nd	xenograft	1 / 0 / 0
Saeed A, 2010 (71)	1	0	1 / 0	1	CS+ CYC	nd	1 / 0 / 0
Da Silva Fucuta Pereira, 2010 (72)	1	1	nd	1	RTX	nd	1 / 0 / 0
Roque R, 2011 (73)	1	0	1 / 0	1	CS+ CPX+PE	nd	0 / 0 / 1
Ignatova TM, 2012 (74)	1	1	1 / 0	1	RTX	nd	1 / 0 / 0
Zaidan M, 2012 (75)	4	2	4 / 0	3	combined therapies°°	nd	2 / nd / nd
Zenone, 2013 (76)	1	0	1 / 0	1	RTX + CS	nd	0 / 0 / 1
Yamazaki T, 2014 (77)	1	0	1 / 0	1	PE	nd	0 / 1 / 0
Harish V, 2014 (78)	1	nd	1 / 0	1	CS+RTX+PE	yes	1 / 0 / 0

MCs: mixed cryoglobulinemia syndrome; HCV: hepatitis C virus; H: healed; U: unchanged; W: worsened; nd: not done
AZA: azatipoprina; CS: corticosteroid; CPX: cyclophosphamide; PE: Plasma Exchange; factor