

Case study

Chronic hepatitis C-related cryoglobulinaemic vasculitis manifesting as non-healing skin ulcers: a case presentation

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Keywords cryoglobulinaemia, vasculitis, hepatitis C virus (HCV), skin ulcers**For referencing** Fraser B. Chronic hepatitis C-related cryoglobulinaemic vasculitis manifesting as non-healing skin ulcers: a case presentation. *Wound Practice and Research* 2020; 28(4):181-188.**DOI** <https://doi.org/10.33235/wpr.28.4.181-188>

Abstract

Aim This paper presents a single case study of hepatitis C virus (HCV)-related cryoglobulinaemic vasculitis (CV) manifesting as non-healing skin ulcers (CV-SU). It discusses ulcer characteristics and management, and highlights the impact of quality of life (QoL) issues faced by the patient.

Background Mixed CV is an extrahepatic immune complex-mediated manifestation of HCV. Vasculitides (cryoglobulins) deposit in the endothelium of small to medium blood vessels in the skin and can lead to ischaemia, necrosis, and SUs or lesions. Cryoglobulins precipitate at temperatures below 37°C, generally in the lower extremities, and redissolve on rewarming. Clinical features include palpable purpura, arthralgia, asthenia and SUs. In severe cases, vasculitis may extend to the lungs, kidneys and nerves.

Methodology The methodology is a descriptive single case study of a 44-year-old male presenting with HCV-induced CV and refractory lower leg ulcers (CV-SU).

Conclusion The management of CV-SU is complex. Resolution requires eradication of HCV, suppression of B cell clonal expansion and cryoglobulin production, and symptom management. The patient's story highlights the importance of understanding and appreciating the lived experience of the condition and the impact of their QoL.

Introduction

Cryoglobulinaemia (CG) is a condition where cryoglobulins (immunoglobulins) precipitate in the tissues at temperatures below 37°C, reversibly dissolving on rewarming¹⁻⁶. Precipitation usually occurs in the lower extremities, with vasculite deposition in the small to medium blood vessels resulting in cutaneous ischaemia and skin lesions or ulcers. The condition is referred to as cryoglobulinaemic vasculitis (CV). Cryoglobulins are associated with infections (e.g. hepatitis C), lymphoproliferative diseases and autoimmune diseases⁷. CG is characterised by a myriad of clinical manifestations including purpura, asthenia, arthralgia and variable organ involvement – kidney, nervous system, gastrointestinal system, interstitial lung involvement and endocrine disorders (diabetes)⁷. Diagnosis may include laboratory findings, histopathology and clinical presentation⁶.

Hepatitis C is associated with several extrahepatic manifestations, some of which affect the skin. The most prominent is CG-induced leukocytoclastic vasculitis or CV and skin ulcers (CV-SU)². CV has a prevalence ranging from 15–50% in patients with chronic hepatitis C virus (HCV), with up to 80% of patients with CV having HCV¹. CG has been identified as an independent factor in liver fibrosis in HCV patients and may be attributed to alcohol consumption and longer disease durations².

The sequelae of HCV-induced CV-SUs and their impact on both health-related quality of life (HR-QoL) and quality of life (QoL), while unquantified, is likely to be significant⁸. The combination of infectious disease and an autoimmune disease may severely impact HR-QoL⁸. Chronic HCV with advanced liver disease alone can be physically and mentally debilitating, while treatment often carries significant physical side effects^{7,9}. CV can have a profound impact on HCV patients, with pain, weakness and lethargy⁸ making activities of daily living difficult for some. Early and timely administration

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with appropriate medical therapy to treat HCV and timely re-treatment of CV if required may ameliorate symptoms of CV, preventing irreversible disability⁸.

Pathogenesis and aetiology of cryoglobulinaemic vasculitis

Several articles have identified a link between HCV advanced liver disease (fibrosis and cirrhosis) and the pathogenesis of mixed CG^{1-5,10}. HCV may be implicated in the low clearance of CG due to the extent of liver damage adding to the severity of the disease¹⁰.

One proposed pathogenesis of CG occurs when dendritic bone marrow cells capture HCV particles and proteins and stimulate the release of B-lymphocytes via a family of B cell activating factors (BAFF)¹⁰. The B cells proliferate and synthesise large amounts of immunoglobulin M (IgM) with rheumatoid factor (RF) activity^{10,11}. The IgM-RF molecules bind the HCV particles and proteins, producing immune complexes that precipitate when cold^{10,11}. Immune complexes bind to endothelial cells of small to medium blood vessels, generating vasoactive peptides, stimulating inflammatory cell recruitment (neutrophils), and mediating leukocytoclastic vasculitis^{10,11}.

CV presents as one of three types – type 1 (monoclonal immunoglobulin without the RF) and types II and III associated with RF-positive monoclonal antibodies (immunoglobulins and complements C3 and/or C4). Types II and III are referred to as mixed CV and are considered a true immune complex mediated vasculitis, with type II commonly associated with HCV⁹.

Pain management

HCV is often associated with advanced liver disease and cirrhosis/fibrosis, limiting pain management options. Pain associated with CV may involve both nociceptive and neuropathic pain pathways, both of which use the same neurotransmitters¹¹. Nociceptive pain (pain caused by a noxious stimulus), however, is adaptive, having biological functions, whereas neuropathic pain does not¹¹. Inflammatory processes recruit nociceptive pain receptors throughout the body, activating somatic pain involving bone, joint, muscle and connective tissue and, in some cases, deeper organs such as the kidneys and lungs¹¹.

HCV treatment is recommended for the eradication of both HCV and CG. While the presence of cryoglobulins does not affect the response to antiviral treatment, antiviral treatment may sometimes be associated with immune-mediated adverse effects such as peripheral sensory/motor neuropathies with associated pain¹¹. Analgesic treatment for CV and background SU pain, in addition to procedural pain, is critical for effective SU management, particularly in more severe non-healing ulcers¹².

Pain management may involve a single drug therapy or a combination of therapeutic agents including biological, NSAIDS, steroidal, analgesic antidepressants, anticonvulsants

and opioids¹¹. Rituximab (a biological agent) has been shown to improve and resolve clinical symptoms of CV, including fatigue, skin manifestations (purpura and SUs), arthralgia and arthritis, and pre-peripheral neuropathies¹¹. For more advanced symptoms of CV with SU involvement, steroids have shown to be effective¹¹. Rituximab is profoundly immunosuppressive and initial management with steroids in combination with HCV treatment should be considered first. In advanced liver disease with cirrhosis and fibrosis, pain management may be limited as a large number of medications are metabolised by the liver. In cirrhotic patients without renal involvement, the clearance rates of many drugs is largely unknown¹¹. With highly protein-binding drugs, low protein and serum albumin levels can lead to increased free drug levels with a concomitant increase in adverse effects and toxicity¹¹. Proposed pain treatment plans are guided by the type of pain present (nociceptive, mixed or neuropathic) and on the liver and renal function¹¹.

This case presentation is important as the literature on HCV-induced CV-SUs and their management is lacking. The overarching therapy and resolution of CV involves eradication of the active HCV. Available literature has identified this condition may significantly impact health and QoL in the long-term⁸. This patient's story is poignant, demonstrating a deep insight into his own circumstance and highlighting QoL issues faced daily. The narrative also reflects how the therapeutic relationship helped the patient to stay resolute in both commencement and continuation of the therapy. Finally, this paper provides an opportunity to contribute to the existing knowledge of individualised treatment options, CV-SU presentation, histopathological findings and wound management.

Methodology

The methodology is a single case study of a 44-year-old male with HCV-induced CV and refractory lower leg ulcers (CV-SU). It is descriptive in nature with a unique focus on the patient's story. Permission was obtained to write this article, to use digital imagery taken throughout the patient's care, and to access their medical record for data relevant to the presentation. Data collection involved reviewing pathology results, reports from scientific investigations and biopsies, duplex scans and wound assessments. Data used was routinely collected and recorded in the patient's electronic medical record as part of their ongoing care and medical management. All data has been de-identified and the patient's anonymity maintained. As this is a single case study with patient permission no ethics approval was sought.

Case presentation

A 44-year old male was admitted to Hospital in the Home (HITH) in July 2019 with several deteriorating deep ulcers to the posterior left calf plus multiple superficial SUs over the remainder of the lower left limb. Known history at this stage was chronic HCV genotype 3a, inherited haemochromatosis (HC) (H63D), ex-intravenous drug use, severe alcohol abuse

(currently a controlled alcoholic), advanced but compensated liver disease with hepatic portal hypertension and ascites. Skin integrity to the right limb was mostly intact; however, there was evidence of scratching secondary to significant pruritus (initially thought to be associated with advanced liver disease and/or venous stasis disease). The patient was diagnosed with the peripheral venous disease after duplex scans identified incompetent veins. There was no arterial compromise.

On examination of the lower limbs, the patient had what appeared to be a venous stasis rash over the dorsum of the right foot (Figure 1A) and bilateral lower limb oedema. No other evidence of dystrophic skin changes consistent with venous stasis disease was noted. The left limb was erythematous and very painful. The ulcers were atypical and not representative of venous stasis ulcers (Figure 1B). Initially, the exudate was dark red frank blood with a strong smell of metallic iron which may have been associated with haemosiderin deposition in the tissues or HC^{13,14}. Haemosiderin is a by-product of the breakdown of the haem protein bound to red blood cells by the body's immune system in the tissues^{13,14}. Connection to mixed HCV-CV was not made at this time due to the atypical rash and diagnosis of venous stasis disease.

Due to the severity of his ulcers and condition of the left lower limb, the patient had been told he may need to have a below knee amputation but was refusing to accept this as an option. Negative pressure wound therapy (NPWT) was applied to the deep ulcers on the posterior left calf with appropriate dressings applied to the remaining ulcers. Bilateral compression therapy was applied to manage the lower limb oedema and support the circulation.

In October 2019, the patient was rushed to the emergency department with bleeding oesophageal varices and haematemesis associated with a relapse of alcohol consumption. At this stage, the deep wounds had granulated sufficiently for NPWT to be ceased, and compression therapy became the mainstay of management in addition to local wound care. The patient was admitted to a neighbouring hospital for 3 weeks for management. On return to our service in November, laboratory work-up identified that the patient's hepatitis C had mutated and re-activated, liver function enzymes (LFTs) were elevated, and the patient was anaemic (secondary to HC). Despite this, his wounds had improved considerably and were almost healed.

The patient was transferred to community nursing for ongoing wound care. The infectious disease (ID) physician remained involved in the management of the patient's HCV and I was no longer involved in his care. Final diagnosis had not been made at this stage; however, on reflection (and in knowledge of the final diagnosis), CG can be initiated by the cold. Compression therapy may have aided in warming his lower limbs, facilitating the dissolution of cryoglobulins and potentially reversing the CV.



Figure 1. Patient's right lower extremity at the time of initial presentation (photos used with permission).

1A. Rash to dorsum of right foot consistent with venous stasis disease.

1B. Left posterior calf showing deep cavity wounds with erythema and swelling. There is evidence of scratching due to pruritus on the lower aspect of the limb. Wounds after 6 weeks of NPWT.

In February 2020, the patient was re-referred to the CNC wound management service. The patient presented with multiple ulcers to the left lower extremity, with moderate sanguineous exudate and a strong smell of iron. Ulcers were present on the right lower limb but not to the same extent nor severity as the left. Over the course of the next couple of months, the left limb swelled and turned a non-blanching deep red/purple colour. Laboratory work-up and clinical presentation are summarised in Table 1.

The ulcers were refractory not responding to any type of management (Figure 2). The wound bed consisted of a moist pitting granulation tissue with a diffuse yellowish necrotic tissue dispersed throughout. At the wound margin this necrotic tissue extended to the sub-cutis and adipose tissue. The wound margins were a deep purple colour with evidence of haemorrhaging under the skin, leading to the progression of a painful necrotic ulcer (Figure 2B). The patient complained of pain particularly in the right lower limb and hands, significant asthenia and weight loss (>20kg). In addition to wound pain, if the lower limbs were cold the pain would radiate to the patient's abdominal area. The patient was admitted to HITH for a medical and ID physician review. On review, the patient had a diffuse maculopapular rash above the left knee and around the dorsum of the foot and there was skin necrosis to the left medial calf (Figures 2A & 2C).

Initially, it was thought the wounds could be secondary to HC, but a literature search failed to find any causal relationship. On initial presentation, the patient presented with a confluent rash without any palpable purpura which appeared more like venous stasis disease. At this presentation the rash was more consistent with a vasculitic process having a diffuse maculopapular appearance. Differential diagnosis of HCV-induced CV manifesting as non-healing ulcers was made and

Table 1. Diagnostic work-up and clinical presentation

Blood pathology	Result	Reference range
Inflammation		
ESR	55mm/hr	(1–10)
CRP	<3	<8mg/LH
Liver function tests		
ALT	46U/L	(10–50)
AST	30U/L	(10–35)
GGT	138U/L	<50
Haemochromatosis		
Iron level	6.4umol/LL	(8–30)
Transferrin	1.9g/L	(1.8–3.5)
Transferrin saturation	15%	(15–45)
Ferritin	202ug/L	(30–400)
Kidney function		
Creatinine	112umol/L	(60–110)
eGFR	68ml/min/1.73m ²	≥90
Other		
Haemoglobin	112g/LL	(130–180)
Platelets	4.2x10 ⁹ /LL	(150–400)
Albumin	30g/L	>35
Diagnostic investigations		
Fibroscan	74kPA	(3.3–78)
HCV load	Log6	<800,000
Duplex scans		
Arterial	No abnormality detected	
CVI	Incompetent superficial veins	
Neurovascular examination		
Dorsalis pedis pulse	Strong	
Capillary refill	<2 seconds	
Temperature	Warm	
Colour	Pink (well perfused)	
Sensation	Full	
Histopathology		
Immunofluorescence microscopy and microscopic examination identified leukocytoclastic vasculitis		
Clinical presentation		
Skin necrosis and ulcers	Chronic HCV	
Asthenia	Liver fibrosis and cirrhosis	
Lower limb oedema	Ex-IVDU	
Maculopapular rash	Controlled alcoholic	
Erythema	Haemochromatosis	
Pain (nociceptive/neuropathic)	Anaemia	
Venous stasis disease	Thrombocytopaenia	

a biopsy of the wounds, skin on the lower limb, and a papule was attended to confirm this diagnosis. Blood pathology was ordered to identify serum cryoglobulins; however, the test had to be cancelled due to the sample being grossly haemolysed.

Histopathology involving immunofluorescence microscopy was performed. The left thigh identified granular deposition of C3 (+) in the superficial dermal vessels and fibrinogen (trace) in the superficial and deep dermal vessels. There was a deposition of fibrinogen (+++) and occasional C3 in the superficial dermal vessels in the right leg. Microscopic examination showed necrosis at the base of the ulcers extending into the underlying dermal connective tissue, with areas of dermal capillary proliferation and haemosiderin deposition. Non-ulcerated skin in the dermis showed acute and chronic perivascular inflammation with focal leukocytoclasia. Fibrinoid necrosis was not seen. There was no evidence of granulomas, dysplasia nor neoplasia. These findings are consistent with vasculitis. The microscopic histopathology examination identified haemosiderin deposition in the tissues which may be due to venous stasis disease or HC or both.

The patient was commenced on topically applied betamethasone cream and oral administration of prednisone (25mg daily) for reducing inflammation and modulating immune properties to resolve the CG as per treatment recommendations. Since commencement of treatment, the ulcers present on the right lower limb have healed. The erythema and swelling to the left lower limb remain; however, several of the smaller ulcers have healed. Resolution of the larger ulcers is dependent on eradicating the patient's HCV and achieving a sustained virological response. Wound maintenance to prevent infection and promote healing continues. In this presentation, full compression therapy and NPWT has not been an option due to lower limb pain. Lighter compression with tubiform is tolerated and assists in supporting the circulation and in keeping the lower limbs warm.

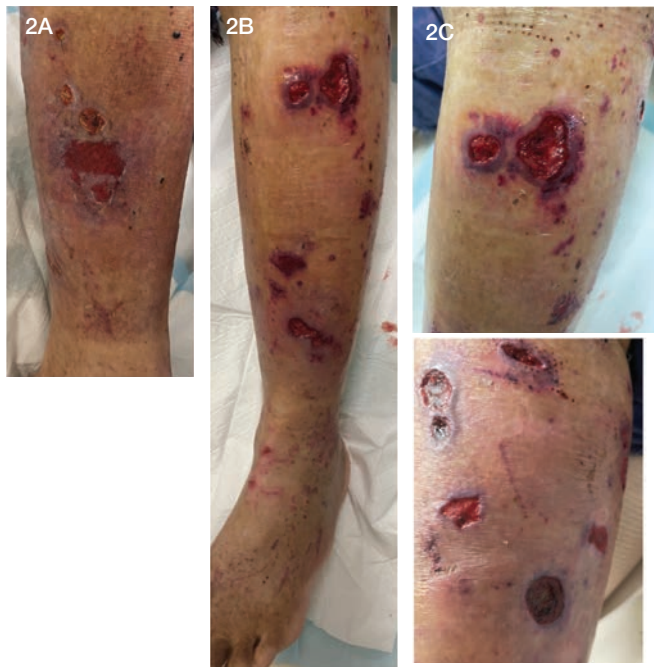
The HCV work-up included a fibroscan and determination of the HCV load. The fibroscan score was 74kPa (a measure of liver stiffness and degree of fibrosis/cirrhosis), equating to F4 on the metavir scale (a measure of the extent of inflammation and fibrosis/cirrhosis of the liver in patients with HCV), with a 90% probability of both fibrosis and cirrhosis.¹⁵ The patient's viral load was Log6 or 1000,000 viral particles. The patient has type 3aHCV with y98h mutation resistant to NS5A polymerase inhibitors. While the patient's fibroscan score is very high, he still has compensated liver failure therefore HCV treatment remains a viable option. Wound management involves interactive dressings according to the condition of the wound bed and perilesional skin. The primary focus is to optimise skin integrity of good skin, protecting existing ulcers from deterioration, preventing infection and maintaining a warm moist healing environment conducive to wound

Figure 2. Patient's lower extremities on second presentation (photos used with permission).

2A. Right lower limb with skin necrosis and ulceration.

2B. Left lower limb with skin ulcers.

2C. Wound presentation.



healing. Keeping the lower limbs warm may also assist in reversing the patient's CG.

The patient's pain is localised to the lower limbs generally and wounds (on dressing changes); however, if the limbs become too cold, the pain progresses up the limbs into the patient's abdomen. Warming cleansing solutions and maintaining room temperature when attending wound care helps to ameliorate this phenomenon. Current pain management is with Tapentadol 150mg modified release and Panadeine Forte. Tapentadol 100mg immediate-release plus topical EMLA cream 5% (5g tube) is used with good effect during wound care. Keeping the limbs warm also assists with pain management. The patient avoids exposing his lower limbs to the cold, wearing long pants and, while sitting or in bed, ensures his legs are covered with a lap blanket or light weight doona.

In this case, there was a missed opportunity to begin treatment for CV early as the rash in the original presentation was thought to be secondary to venous stasis disease. Even though the ulcers were not representative of the condition, the mainstay of management was compression therapy. The deep ulcers to the posterior calf were successfully managed with NPWT. With a definitive diagnosis, hopefully, we can work with this patient to eradicate his HCV, resolving his CV, and improving not only his HR-QoL but QoL generally.

After several discussions with the ID physician and the CNC wound management service, the patient has decided to go

ahead with the HCV treatment. Inclusion of the patient in the decision-making process was pivotal if the proposed therapy was to be successful. Treatment commenced in August 2020 using the DOT (Directly Observing Therapy) care delivery model¹⁶. Treatment consists of a combination of direct-acting antiviral medication SOF/VEL/VOX (Sofasbivir/Velpatasvir/Voxilaprevi) plus Ribavirin⁹. Blood work-up for LFTs, FBC, EUC and ESR will be repeated in preparation for the treatment, and the blood will be closely monitored throughout the program. The patient's CG and CV will initially be managed with Prednisone 25mg daily.

Since commencing oral prednisone (August 2020) the majority of wounds have healed, with the exception of those located on the posterior left calf (Figure 3A–D). These wounds have progressively deteriorated and are not responding to steroid therapy. Objective wound assessments using MEASURE¹⁷ are conducted regularly in addition to digital imaging to monitor wound deterioration. A second biopsy (late September 2020) was attended to further investigate the nature the ulcers and to look for causative agents (fungi and microbacteria; acid fast bacilli) of the foreign body giant cell (FBGC) reaction identified in the first biopsy. However, no additional information was forthcoming other than to re-confirm a vasculitic process – skin tissue with ulceration, chronic inflammation, formation of granulation tissue, abundant haemosiderin pigment and FBGC reaction. There is infiltration of the inflammatory cells in the walls of the blood vessels of the sub-cutis (neutrophils, lymphocytes and plasma cells) that extends through the adipose tissue.

The presence of a FBGC reaction – caused by the clumping of monocyte-macrophages – may explain the progressive wound deterioration as this has been demonstrated to contribute to chronic inflammatory processes and progressive tissue destruction through the release of proteolytic degradative enzymes and excess reactive oxygen species (ROS)¹⁸. Wound management will be tailored to rebalancing these enzymes and reducing the levels of ROS to promote healthy granulation tissue growth.

The patient's mental health has also deteriorated secondary to the steroid therapy. Eight weeks into the treatment to patient complained of experiencing unhealthy thoughts. These thoughts consisted of flash backs to unhappy lived experiences and forgotten memories or events that were addressed and locked away. The impact of these thoughts was such that the patient considered physically harming himself and was having suicidal tendencies. Medications such as steroids, while a first choice for treatment of CV, can be a confounding factor for poor mental health, interfering with thought processes having potentially significant deleterious side effects.

Due to the poor response of the wounds to steroid therapy and in light of the side effects of the medication on the patient's mental health the plan is now to wean the prednisone and add Rituximab^{5,9,11,12,13} to the treatment

regime. The patient is about to commence the final course of his HCV treatment.

I will continue to be involved in his care, monitoring treatment progress and hopefully see the eradication of his HCV and resolution of his CV and related SUs.

Patient's story

The patient's story is outlined below.

I have lived with chronic hepatitis for a long time. It's my fault as I was an intravenous drug user and an alcoholic (still am but controlled). These ulcers on my legs have been there for about a year now and have caused me considerable grief. I am fortunate to have such strong support from the people who look after me on so many levels. They listen to me and don't judge me. Without that support, I would not get through this.

The condition that has caused these ulcers and my HCV combined has severely impacted my health and quality of life. Some days I am unable to get out of bed due to fatigue and weakness. The pain in my lower legs and hands is very debilitating, and pain-relieving options are limited due to my advanced liver disease. At times I feel as though I need to increase my alcohol consumption to temper my anxiety and depression, especially on bad

days but I know if I have another episode of oesophageal bleeding I may not survive.

I am the carer for my partner and stepson, both of whom have significant health and mental health issues. Trying to run a household and take care of them becomes impossible at times. Having hepatitis C, CV and advanced liver damage have depleted my capacity to live a healthy life. I am a controlled alcoholic and have lowered my alcohol consumption as low as I can possibly get it, even though it is hard sometimes not to have just one more drink. I understand that the Hep C treatment I am about to start could have serious side effects (more so if I don't control my drinking) or fail but, if successful, it will send me into remission for a second time, giving me another chance to live a longer and healthier life. Not having to put up with the pain and fatigue caused by these ulcers and my hepatitis will be life-changing for me.

Conclusion

CG is a condition arising when cryoglobulins (immune complexes such as IgM-RF) deposit in small to medium blood vessels in the skin. The resulting vasculitis causes an inflammatory process characterised by infiltration of inflammatory cells (neutrophils, lymphocytes and plasma cells) leading to vascular damage and leucocytoclasia. While

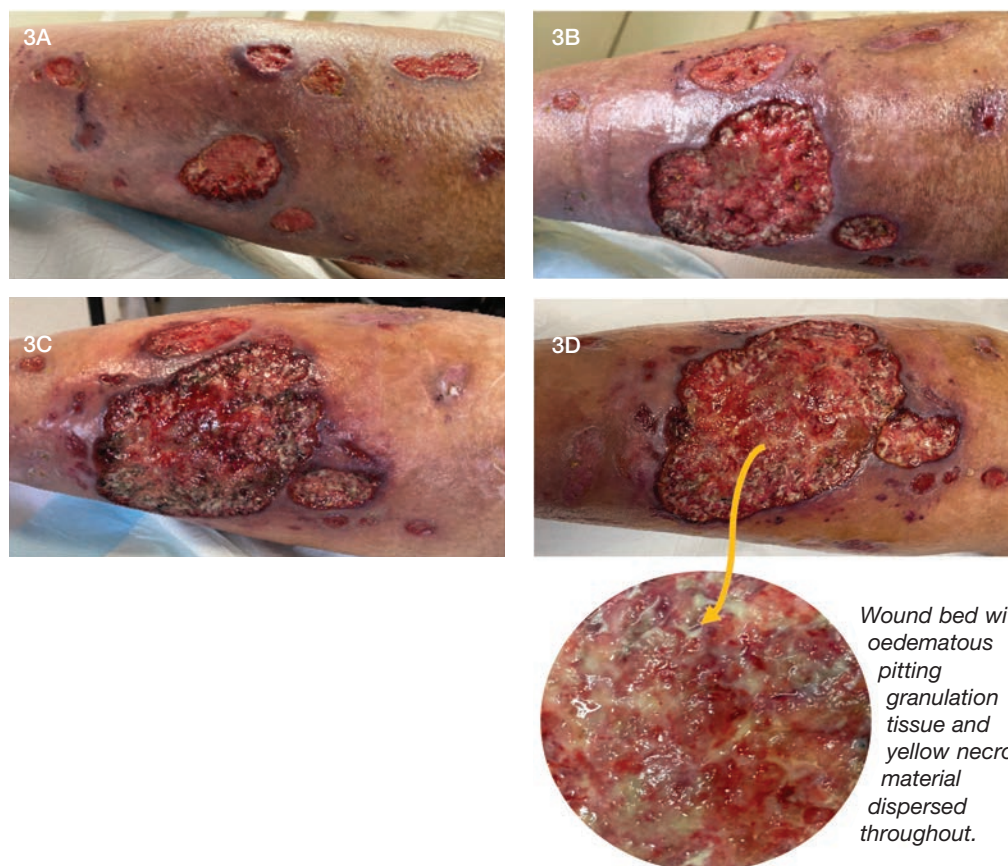


Figure 3. Photos of left posterior calf showing progressive deterioration of the wounds (photos used with permission).

3A. August 2020

3B. September 2020

3C. 2 October 2020

3D. 9 October 2020

Periwound margins with subdermal haemorrhage and chronic inflammation causing progressive tissue destruction resulting in wound progression is clearly seen. Skin necrosis extends into the sub-cutis and adipose tissue.

HCV-related CV and their management is well documented in the literature, information regarding the nature of associated skin lesions or ulcers and their management is limited. Holistic assessment and diagnostic work-up is pivotal to diagnosis. Assessment of the patient's general health and wellbeing, HCV virology, histopathology of the SUs and papura, full blood work-up and wound assessment provides valuable information to guide management.

For this case presentation, overarching management has been the administration of direct-acting antivirals to eradicate HCV and steroids to manage the CV. Due to the poor response of the SUs to treatment and the deleterious side effect of the prednisone on the patient's mental health, weaning has commenced, with the plan to add Rituximab to the treatment regime. Rituximab acts to deplete monoclonal antibodies (CD-20) causing the CG and treating the SUs not responding to therapy. Management of the SUs is tailored to the wound characteristics. Interactive dressings, debridement, control of inflammation and/or infection, and maintaining moisture balance are essential therapeutic goals. Assessment of background SU pain and procedural pain is essential to successful management. As the patient's level of liver damage excludes many pain management options, keeping his lower limbs warm is a crucial element.

The patient's story is poignant, highlighting the impact of the condition and its sequelae on both his HR-QoL and QoL. Chronic illness, pain, weakness and lethargy has profoundly impacted the patient's mental health and limited his capacity to carry out daily activities. Medications such as steroids, while a first choice for treatment of CV, can be a confounding factor for poor mental health, interfering with thought processes and having potentially significant deleterious side effects. Treatment becomes a fine balance between achieving the desired therapeutic goal and maintaining the psychological and physical safety of the individual. This case presentation brings to light the complexity of managing both CV and CV-SUs. Treatment must be person-centred and tailored to the individual's needs. Successful resolution of CV and CV-SUs is dependent on eradication of the underlying cause.

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Conflict of interest

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Patient consent

Obtained.

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THANK YOU

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