Elsevier Editorial System(tm) for Journal of Tissue Viability
Manuscript Draft

Manuscript Number: JTV-D-13-00006R1

Title: Cutaneous ulcers associated with hydroxyurea therapy

Article Type: Review of clinical or scientific aspects

Keywords: cutaneous ulcers; hydroxyurea; hydroxyurea induced ulcers.

Corresponding Author: Prof. Marco Romanelli, MD PhD

Corresponding Author's Institution: University of Pisa

First Author: Filippo Quattrone

Order of Authors: Filippo Quattrone; Valentina Dini, MD, PhD; Sabrina Barbanera, MD; Nicola Zerbinati, MD; Marco Romanelli, MD, PhD

Abstract: Abstract

Hydroxyurea is an antitumoral drug that acts as an inhibitor of ribonucleotide reductase, an enzyme essential for DNA synthesis. It is used in the treatment of Philadelphia-chromosome negative mieloproliferative syndromes, sickle cell disease, psoriasis, some solid cancers and in the treatment of HIV infection.

Due to its direct cytotoxicity and its photosensitising action, Hydroxyurea is responsible for a wide spectrum of cutaneous side effects. These include: xerosis, ichthyosis, skin atrophy, facial erythema, palmoplantar keratoderma, alopecia, skin hyperpigmentation, dermatomyositis-like eruptions, onychodystrophy, melanonychia, actinic keratoses, squamous cell carcinomas and leg ulcers which are a rare but severe long-term adverse effect of hydroxyurea therapy.

Hydroxyurea-induced leg ulcers appear usually as small, well-defined, shallow ulcers with an adherent, yellow, fibrinous necrotic wound bed. They are typically found in the perimalleolar region but also on the heel, dorsum of the foot and the toes; occasionally forearms, hands and face can be affected. Lesions are often multiple and bilateral. A constant finding is an extreme, difficult-to-treat pain accompanying the ulcerations. The withdrawal of the drug generally leads to spontaneous healing of these lesions.

Care providers have scarce awareness of this cutaneous side effect and late or wrong diagnoses are frequent. Indeed, regular dermatologic screening should be performed on patients treated with hydroxyurea.

A review of indexed case reports and clinical studies was made to increase information on this specific topic.

Azienda Ospedaliero Universitaria Pisana
OSPEDALE DI RILIEVO NAZIONALE E DI ALTA SPECIALIZZAZIONE

U.O. DERMATOLOGIA UNIVERSITARIA
Direttore: Prof. G. Cervadoro

Pisa, 16 March 2013

To the Editor of the Journal of Tissue Viability

Object: Cutaneous ulcers associated with hydroxyurea therapy

Dear Editor,

We are happy to submit the review paper in the object as a contribution for a special issue on atypical wounds

This is to certify that all the authors have made substantial contributions to all of the following:

- The concept and design of the study, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval for the version to be submitted

Yours Sincerely,

Prof. Marco Romanelli

Via Roma, 67 – 56126 PISA - Tel. 050.553450 – Fax 050/551124 – E-mail: segr-dermo@med.unipi.it

***Response to reviewers**

The authors like to thank the reviewers for the interesting comments. The authors like also to point out the discrepancies between comments from two reviewers.

Below are the answers to comments received

Reviewer #1

- The authors have reduced the description of different cutaneous adverse effects

- The authors have included several new figures and tables which summarize the concept of the review

- Figure 2 was showing not only erythematous papules but also several ulcers covered by fibrin (yellow colour). Despite that misunderstanding from reviewers the authors have decided to change the picture with a new one

- Tables have been included to list the postulated pathogenetic mechanism of HU-induced leg ulcers

- Grammatical and stylistic errors have been corrected

Reviewer #2

-tables have been included

The authors have no conflict of interest

The authors have no conflict of interest

***Title page with author details**

Cutaneous ulcers associated with hydroxyurea therapy

Filippo Quattrone

Valentina Dini, MD, PhD*

Sabrina Barbanera, MD*

Nicola Zerbinati, MD°

Marco Romanelli, MD, PhD*

Istituto Superiore S. Anna, Pisa

*Department of Dermatology, University of Pisa

°Department of Surgical and Morphological Sciences, University of Insubria

Correspondence:

Dr. Marco Romanelli
Department of Dermatology
University of Pisa
Via Roma, 67
56126 Pisa
ITALY
Tel +39 050 992436
Fax +39 050 551124
m.romanelli@med.unipi.it

Abstract

Hydroxyurea is an antitumoral drug mainly used in the treatment of Philadelphia chromosome-negative myeloproliferative syndromes and sickle-cell disease. Ulcers represent a rare but severe long-term adverse effect of hydroxyurea therapy.

Hydroxyurea-induced ulcers are often multiple and bilateral, typically developing in the perimalleolar region, although any cutaneous district is potentially affected. They generally look small, well-defined, shallow with an adherent, yellow, fibrinous necrotic base. A constant finding is also an extremely intense, treatment-resistant pain accompanying these ulcerations. Withdrawal of the drug generally leads to spontaneous healing of these lesions.

Care providers tend to show insufficient awareness of this highly debilitating cutaneous side effect, and late or missed diagnoses are frequent. Instead, regular dermatologic screening should be performed on hydroxyurea-treated patients.

This article will present a comprehensive review of indexed case reports and clinical studies, followed by a discussion about treatment options aiming at increasing knowledge about this specific topic.

Introduction

Cutaneous ulcers represent a pathology typical of the lower limb, due to the anatomy of its terminal circulation, and are usually caused by arterial insufficiency, venous stasis or metabolic diseases such as diabetes. Ulcers are common as well in myeloproliferative disorders (MPDs) and in sickle cell disease (SCD), due to the alteration of microcirculation typical in these conditions (1). Also drugs, including hydroxyurea (HU), can be a rare cause of ulcers (2).

Hydroxyurea pharmacological properties and mechanisms of action

HU or hydroxycarbamide, firstly synthesized in 1869 by Dresler and Stein from hydroxylamine and hydrogen cyanate (3-4), is a non-alkylating hydroxylated urea analog with antineoplastic and antiviral properties (5). It is indicated in the treatment of Philadelphia-chromosome negative myeloproliferative syndromes (MPs), sickle cell disease (SCD), psoriasis (6), some solid cancers and it was proposed in combination with antiretroviral drugs in the therapy of HIV infection (7).

HU is an easily absorbed drug and reaches peak blood levels 1–2 hours after ingestion. It has an almost complete bioavailability and distributes in the water compartments of the body so that intravenous administration is usually unnecessary. It can cross the blood–brain barrier and the placenta, and can be found in breast milk. it is eliminated mainly through the kidneys (5).

HU was a pioneer drug in the treatment of solid cancer, but unlike the other first generation-chemotherapeutics is not a metabolite analog; it is instead a non-competitive inhibitor of the enzyme ribonucleotide reductase (RR), which is essential for the synthesis of deoxyribonucleotides from ribonucleotides. Inhibition of RR results in depletion of desoxyribonucleotides (dNTPs), cessation of DNA synthesis and death of S-phase cells. Moreover, HU can bind and inhibit another enzyme, histone deacetilase, thus inducing differentiation of tumoral cells via c-jun expression (8). Also, HU induces sensitization of tumors to other chemotherapeutic agents through a yet

different mechanism: the depletion of dNTPs facilitates the activity of pyrimidine and purine antimetabolites; RR also plays a role in DNA repair, therefore HU is associated with dsDNA breaks; HU could possibly help reverse acquired tumoral resistance to chemiotherapy promoting loss of extrachromosomal-amplified genes (5).

Hydroxyurea systemic and dermatological side effects

Despite its reputation of being a safe drug, the reported adverse events during HU treatment are numerous and concerning different body systems; not surprisingly, tissues with high cell turnover are the most affected by the cytostatic action of HU.

HU can affect bone marrow causing myelosuppression, bleeding and, rarely, leukemic transformation. B12 or folate-unrelated macrocytosis can occur. Oral mucosal ulcerations and pigmentation, accompanied by nausea and vomiting, epigastric pain and diarrhea represent the most common reported gastrointestinal side effect of HU therapy (5-9). Ulcers of genital mucosa have also been described (10,11). High fever outbreak sometimes associated with maculopapular rash and abnormal liver function tests (12), pneumonitis and bronchiolitis obliterans (13), vasculitis (14) and gangrene in toes (15-16) have also been reported in literature as HU possible adverse effects.

HU therapy has been associated with multiple cutaneous alterations (Table 1) such as xerosis, scaling, atrophy of the skin and subcutaneous tissues, skin hyperpigmentation, facial and acral erythema, palmoplantar keratoderma, solar hypersensitivity with eruptive appearance of squamous cell and basal cell carcinomas on sun-exposed sites, partial non-cicatricial alopecia, nail alterations and cutaneous ulcers (Fig. 1) (17).

To this range of cutaneous complications should also be added a characteristic eruption, unique to patients affected by hematologic malignancies, described in the literature through multiple names: lichen planus-like lesions (18,19), dermatomyositis-like lesions, pseudo-dermatomyositis, Gottron-like papules, dermatomyositis without myositis (20-23) as well as being associated with graft-versus-host disease (24). Daoud proposed recently the definition of hydroxyurea dermopathy for this unique nosological entity (25). It is characterized by a poikilodermatous eruption with telangiectasia, erythema, scaling, and lichenoid papules resembling Gottron's papules of dermatomyositis, usually on the dorsa of hands and knuckles.

HU-induced non-melanoma skin cancer usually occurs in clear Fitzpatrick phototype-patients affected by hematologic malignancies. HU expresses its carcinogenic potential

by preventing the repair of light exposition-induced DNA damage, thus leading to cellular dysregulation and solar hypersensitivity, with spectrum of skin changes that extends from sunburn to non-melanoma skin cancers (26). The presence of Bowen's disease and multiple actinic keratoses in sun-exposed areas that can evolve to multiple aggressive squamous cell carcinomas (27,28) is typical. The category of "HU-associated squamous dysplasia" has been used to describe these premalignant lesions (28).

Nail changes are probably an underestimated finding in patients on hydroxyurea. They include onychodystrophy, generalized hyperpigmentation (melanonychia), longitudinal bands and blue lunulae. Nail dyschromy develops predominantly in female patients and the thumb and index fingernails appear to be the most frequently affected sites. Longitudinal bands are the most common pattern, while transverse melanonychia is probably related to intermittent courses of chemotherapy, due to the direct toxic effect on the nail matrix. These changes have been variably related to genetic predisposition, the toxic effect of hydroxyurea on the nail bed and matrix, photosensitization, and focal stimulation of melanocytes at the matrix level (29-30).

Cutaneous ulcers during HU therapy, firstly described by Stahl and Silber in 1985 (31), are still today a poorly recognized side effect of this drug, despite them alone accounting for 30% of all dermatologic adverse events reported to the manufacturer worldwide (1). Their prevalence in clinical studies is variable: from 3,5%-5% in large cohort studies (32-35) to 8,5-10% or even more in studies with smaller numbers of participants (36-43). Due to their impact on treated patients' health and quality of life, cutaneous and mucosal ulcers, together with fever, pneumonitis and any mucocutaneous alterations unacceptable for the patient, were recently included by an international consensus conference in the definition of clinical intolerance to HU (35,43).

Clinical feature and pathogenesis of hydroxyurea associated cutaneous ulcers

Hydroxyurea-induced cutaneous ulcers are usually small, well-defined and shallow with an adherent, yellow, fibrinous necrotic base (Fig. 2) (44). They are typically found in the perimalleolar region but also on the lower leg, heel, dorsal foot and toes; occasionally forearms, hands and face can be affected (35). Skin lesions are often multiple and bilateral. Lesions are surrounded by a livid erythema and areas of small white scars called atrophie blanche (2). A constant finding is an extremely intense, treatment-resistant pain accompanying these ulcerations, often requiring the administration of

opioids. Extension of such lesions seems directly correlated in the individual patient to HU dosage (1). The histology of the lesion is usually aspecific, but may show epidermal atrophy, dermal fibrosis, scar tissue without vasculitis and, occasionally, fibrinoid thrombi (table 3) (45).

The mechanisms underlying the pathogenesis of the HU-associated cutaneous ulcer are not clearly defined, but probably various different elements play a role in their occurrence (Fig. 3) (46). Defective repair mechanisms in skin basal cells due to HU cytotoxicity undoubtedly plays a role in the formation of leg ulcers as well in the pathogenesis of all dermatologic HU side effects. Long term HU therapy leads to cumulative cytotoxicity for the basal cells of the epidermis, due to inhibition of DNA synthesis and formation of free radicals. The injury progresses until cellular repair mechanisms are no longer able to regenerate keratinocytes and endothelial cells (47-48). This is partially confirmed by the finding, in an autoradiographic study of patient on hydroxyurea, of large areas of absent epidermal uptake of tritiated thymidine (49). Moreover most authors believe that minor traumas, very common in malleolar areas as caused by shoes, have a role as initiating factors in ulcer development. Few patients, however, report traumas during anamnesis (50-51). Some authors have argued that the pathogenesis of HU-associated leg ulcers is related to ischemia following intravascular thrombosis (52). It has been speculated that HU associated with blood dyscrasia in MPDs may induce a procoagulative status in the malleolar vessels and cause cutaneous atrophy (52). However, ulcerative skin lesions appear in MPDs after the blood count is well controlled by HU and, paradoxically, improve when blood dyscrasia recurs (53). This hypothesis is therefore no longer widely accepted. Macrocytosis is now considered to be a major pathogenic factor (54). The megaloblastic changes in erythrocyte geometry and deformability caused by HU may prevent these cells from easily traversing the capillaries. This may impair blood flow in the microcirculation and cause relative ischemia in the basal layer of the skin, which requires more oxygen for proliferation (55). The anoxic state and the formation of microthrombi could account for the extreme painfulness of these lesions. Concomitant arterial, venous or metabolic disease may play an additional role in the development of such wounds. In differential diagnosis vasculitis, cryoglobulinemia and pyoderma gangrenosum should be considered if typical clinical signs are demonstrated (1). A summary of significant anamnestic, clinical and instrumental findings relevant to the diagnosis of HU-induced ulcer is presented in Table 2.

Hydroxyurea-induced ulcers: data from a review of case reports and clinical studies

In this section we present the results of a review of case reports and clinical studies made with the aim of summarising the published literature on HU-induced ulcers. MEDLINE and TOXLINE databases were searched and 82 articles were selected for examination: 74 case reports, 5 retrospective clinical studies, 3 prospective clinical studies. Data extraction focused on the following variables: medical history (patient gender, age, underlying pathologies; presence of venous or arterial insufficiency, diabetes, hypertension, report of previous trauma in the site of lesion or other cutaneous manifestations due to HU treatment); pharmacological anamnesis (duration of HU therapy, HU daily and cumulative dose, co-use of interferon or other drugs); ulcer feature (site of lesions, presence of multiple or bilateral lesions, duration of ulcer before correct diagnosis); Therapy of the underlying disease and of the lesion (HU withdrawal, substitutive hematologic therapy, healing therapy, time of ulcer healing, outcome).

407 cases of HU-induced leg ulcers were found described in the literature. Leg ulcerations were found to be more common in females than males (193 females/164 males/ 50 not reported). The mean patient age was 62,7 years (range 21-84). The population with MPDs was significantly older (mean 64 years) than SCD patients (mean 37,3 years). Underlying pathologies were distributed as follow: 102 chronic myelogenous leukemia (CML) patients, 82 policytemia vera (PV) patients, 134 essential thrombocythemia (ET) patients, 26 myelofibrosis (MF) patients, 8 SCD patients, 4 undifferentiated MPDs, 1 case of psoriasis (56). It is significant that a similar number of cases was found among the most common MPDs. Risk factors for leg ulcers were found in some patients (37 case of venous insufficiency, 30 cases of arterial insufficiency, 15 diabetic patients, 54 patients with hypertension). 24 patients had multiple risk factors. These data confirm the concept that HU exposure alone is sufficient to cause the insurgence of ulcers. However, before HU treatment is stopped, other risk factors for leg ulcers development should be carefully ruled out since cases of venous ulcers mimicking HU-induced lesions have been reported (1,57,58).

Minor traumas before ulcer formation were reported during anamnesis by only 27 patients. However, the preponderance of lesions in the lateral side of the lower limb (75% of lesions reported to be lateral or medial) strongly suggests a role of minor

traumatic events in HU-induced ulcer pathogenesis. Patients can sometime refer a history of previous ulcers spontaneously healed during HU treatment (59). The coexistence of ulcer with other dermatological side effects of HU, most frequently atrophic skin changes and nail alterations, is quite a common finding (41) reported in 62 patients in our survey.

More than half of the lesions (59,4%) were in the perimalleolar region. Heel ulcerations were detected in 10,7% of patients, leg lesion in the 11,5%. Toe lesions and the dorsal foot were affected in 6,6% each of cases. Ulcerations of Achilles tendons and hands (respectively 1,7% and 3,4%) were rare. Two cases of forearm ulceration (60, 61) and another of post-operative ulcer (62) were reported. Bilateral lesions were present in 31% of patients showing in this way the systemic nature of HU noxa. Infection and malignant transformation of HU-induced leg ulcers have been reported in literature (45, 63).

Ulcer insurgence was associated with any daily dosage of HU. The mean dose is about 1,5 g. In 9 cases even the lowest dose administrable, 0.5 g/die, proved to cause leg ulcerations. This is in contrast with Bader, and many authors following him, who stated that 1 g was the lowest dose associated with HU dermatologic side effects (1). The mean cumulative dose was 1733 g (range 510-3960 g). The median duration of HU therapy before ulcer formation was about of 51 months (range 1.75 – 215 months). In 2006 the FDA highlighted an increased risk of ulceration in patients with a history of, or currently receiving, interferon therapy. In our review only 20 patients reported a positive history for use of interferon and hydroxyurea.

Case reports showed a median diagnosis delay of 8 months. When lesions are recognized as HU-induced ulcers, drug withdrawal and local wound care is the most common therapeutic choice (79%) with a rate of 99% of healing. However, different authors report treatment of HU-induced ulcer without withdrawal: dose reduction, even transient (64), intermittent schedules (65), accurate debridement and wound management (66,67) have been suggested to boost the ulcer healing process. In addition to pharmacologic adjustments, in order to successfully expedite wound healing, the use of advanced wound-care products (Table 4) has been described. Even skin grafts and hyperbaric oxygen have been used successfully (46,59,76). Not stopping HU treatment in presence of leg ulcers appear associated with an higher risk of absent or incomplete healing (18%) and therefore should be advised only in patient that cannot stop HU.

Our survey found that the median healing time after HU withdrawal or dose reduction

was 150 days (range 13 - 2,160). Many substitutive therapies have been used to replace HU: anagrelide, phlebotomy, aspirin, busulfan, interferon alpha, pipobroman, imatinib cyclophosphamide. Anagrelide too, however, can cause ulcers and a case of anagrelide-induced relapse of a HU-induced leg ulcer has been reported (60). Recidives of ulcers after HU withdrawal, even after five months from stopping, were reported and ascribed to HU accumulation in the site of the lesion and lack of inadequate debridement of wounds (52, 75).

In conclusion we present a clinical flowchart (Fig. 4) for the treatment of HU-induced ulcer with the aim to help correct diagnosis and effective therapy avoiding invasive and useless examination to the patient.

Discussion

HU-induced ulcers represent a serious threat in terms of disability and loss of quality of life in affected patients. The ulcerations are often multiple, recidivating and painful, with risk of neoplastic transformation. Moreover, the literature reports a high amount of delayed diagnosis due to the confusing comorbidities of these patients. An increased awareness on the part of care providers is therefore needed to prevent this adverse effect and the high care cost it causes.

To reach an efficacious early prevention, multiple strategies are possible (see Tab): firstly, patients with risk factors for leg ulcers such as diabetes and venous insufficiency should be considered, if possible, for other treatments apart from HU or should be attentively monitored during therapy. In addition, hematologists should inform patients and their relatives about the increased risk of cutaneous ulcers and photosensitivity due to HU, suggesting opportune leg protections and solar filters. Moreover dermatologic evaluation and, for suspect lesions, dermatologic consultation should be regularly performed by the hematologist, especially after long periods of treatment. This could help the individuation of early stages of the disease, allowing a precocious discontinuation of the drug.

A recent study showed in ET subjects a correlation between poor survival and the development of ulcers during HU therapy. Authors proposed that underlying vasculopathy has predisposed these individuals to both ulcer development and cardiovascular accidents. A cardiovascular screening, therefore, may be advised for these patients, especially before switching to anagrelide, which is reported to have cardiovascular side effects (77).

An interesting issue needing further evaluation is related to the dermatological effects of HU in sickle cell disease. HU for the treatment of SCD was approved in 1998 and it is

considered the only treatment for sickle cell disease that modifies the disease process. In contrast with MPDs, in which HU is given for short periods to white adult patients, HU in SCD is administered on a lifelong basis to young black patients. HU-induced ulcers in SCD patients have been described in clinical studies (79, 80) and some case reports (81,82). The first of these studies found a rate of HU-induced leg ulcers (29%), higher than that reported in MPD patients, especially in patients with a previous history of leg ulcers (79). However, a randomized controlled studies and a systematic review (62), did not find any association between HU and leg ulcers in SCD population (78, 83). Probably further randomized controlled studies will be necessary in order to definitely confirm or exclude this correlation (84).

References

1. BADER U, BANYAI M, BÖNI R, BURG G, HAFNER J. Leg ulcers in patients with myeloproliferative disorders: disease or treatment-related? *Dermatology*. 2000; 200: 45-48.
2. DISSEMOND J. Medications. A rare cause for leg ulcers. *Hautarzt.* 2011; 62: 516-523.
3. DRESSLER W, STEIN R. [About Justus Liebig‘s hydroxylurea]. *Ann. Chem. Pharm.* 1869; 150: 242–252.
4. MATHEWS CK. DNA synthesis as a therapeutic target: the first 65 years, *FASEB J*, 2012; 26: 2231-2237.
5. SPIVAK JL, HASSELBALCH H. Hydroxycarbamide: a user's guide for chronic myeloproliferative disorders. *Expert Rev Anticancer Ther*, 2011;11: 403-414.
6. YARBRO JW, LEAVELL UW. Hydroxyurea: a new agent for the management of re-fractory psoriasis. *J Ky Med Assoc.* 67(1969) 899-901
7. LORI F, MALYKH A, CARA A, SUN D, WEINSTEIN JN, LISZIEWICZ J, GALLO RC. Hydroxyurea as an inhibitor of human immunodeficiency virus-type 1 replica-tion. *Science* 266 (1994) 801-5
8. ADUNYAH SE, CHANDER R, BARNER VK, COOPER RS, COPPER RS. Regulation of c-jun mRNA expression by hydroxyurea in human K562 cells during erythroid differentiation, *Biochim Biophys Acta*, 1995; 22: 123-132.
9. PALERI V, LINDSEY L. Oral ulcers caused by hydroxyurea*. J Laryngol Otol*. 114 (2000) 976-7
10. KELLY RI, BULL RH, MARSDEN A. Cutaneous manifestations of long-term hydroxyurea therapy. *Australas J Dermatol*. 35(1994) 61-4
11. KARINCAOGLU Y, KAYA E, ESREFOGLU M, AYDOGDU I. Development of large genital ulcer due to hydroxyurea treatment in a patient with chronic myeloid leukemia and Behcet's disease. *Leuk Lymphoma*. 44 (2003) 1063-5
12. LANNEMYR O, KUTTI J. Hydroxyurea as a cause of drug fever in essential thrombocythaemia. *Eur J Haematol.* 62(1999) 354-5
13. KALAMBOKIS G, STEFANOU D, ARKOUMANI E, KITSANOU M, BOURANTAS K, V TSIANOS E. Fulminant bronchiolitis obliterans organizing pneumonia following 2 d of treatment with hydroxyurea, interferon-alpha and oral cytarabine ocfosfate for chronic myelogenous leukemia. *Eur J Haematol*. 73(2004) 67-70
14. YOUNG HS, KIRBY B, STEWART EJ. Aggressive, extensive, vasculitic leg ulceration

associated with hydroxyurea therapy and a fatal outcome. *Clin Exp Dermatol*. 2001; 26:664-7
15. YASUDA N, OHMORI S, USUI T. Hydroxyurea-induced gangrene of the toes in a patient with chronic myelogenous leukemia. *Am J Hematol*. 2000; 63:103-104.
16. LEO E, KRÄMER A, HOCHHAUS A, KRASNIQI F, HEHLMANN R, HO AD. Gangrene of the toes in a patient with chronic myelogenous leukemia after long-term hydroxyurea therapy. *Ann Hematol*. 2002; 81:467-9.
17. NOFAL A, EL-DIN ES. Hydroxyurea-induced dermatomyositis: true amyopathic dermatomyositis or dermatomyositis-like eruption? *Int J Dermatol*. 2012; 51:535- 541.
18. KENNEDY BJ, SMITH LR, GOLTZ RW. Skin changes secondary to hydroxyurea therapy. *Arch Dermatol*.1975; 111: 183-187.
19. BOHN J, HANSEN JP, MENNÉ T. Ulcerative lichen planus-like dermatitis due to long-term hydroxyurea therapy. *J Eur Acad Dermatol Venereol*.1998; 10: 187-189.
20. SENET P, ARACTINGI S, PORNEUF M, PERRIN P, DUTERQUE M. Hydroxyurea-induced dermatomyositis-like eruption. *Br J Dermatol*. 1995; 133: 455-459.
21. VASSALLO C, PASSAMONTI F, MERANTE S, ARDIGÒ M, NOLLI G, MANGIACAVALLI S, BORRONI G. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol*. 2001; 26: 141-148.
22. BAHADORAN P, CASTANET J, LACOUR JP, PERRIN C, DEL GIUDICE P, MANNOCCI N, FUZIBET JG, ORTONNE JP. Pseudo-dermatomyositis induced by long-term hydroxyurea therapy: report of two cases*. Br J Dermatol*. 1996; 134:1161-1163.
23. MARIE I, JOLY P, LEVESQUE H, HERON F, COURVILLE P, CAILLEUX N, COURTOIS H. Pseudo-dermatomyositis as a complication of hydroxyurea therapy. *Clin Exp Rheumato*l. 2000; 18: 536-537.
24. EMING SA, PETERS T, HARTMANN K, SCHARFFETTER-KOCHANEK K, MAHRLE G. Lichenoid chronic graft-versus-host disease-like acrodermatitis induced by hydroxyurea. *J Am Acad Dermatol*. 2001; 45: 321-323.
25. DAOUD MS, GIBSON LE, PITTELKOW MR. Hydroxyurea dermopathy: a unique lichenoid eruption complicating long-term therapy with hydroxyurea. *J Am Acad Dermatol*. 1997; 36: 178-182.
26. TURNER ML. Sun, drugs, and skin cancer: a continuing saga. *Arch Dermatol*.2010; 146: 329-331.
27. ASTE N, FUMO G, BIGGIO P. Multiple squamous epitheliomas during long-term treatment with hydroxyurea. *J Eur Acad Dermatol Venereol*. 15 (2001) 89-90
28. SANCHEZ-PALACIOS C, GUITART J. Hydroxyurea-associated squamous dysplasia*. J Am Acad Dermatol.* 2004; 51: 293-300.
29. ASTE N, FUMO G, CONTU F, ASTE N, BIGGIO P. Nail pigmentation caused by hydroxyurea: report of 9 cases*. J Am Acad Dermatol*.2002;47:146-147.
30. SU PH, HOW CK, YEN DH, HUANG MS. Melanonychia secondary to hydroxyurea*. Intern Emerg Med*. 2012; 7:289-290.
31. STAHL RL, SILBER R. Vasculitic leg ulcers in chronic myelogenous leukemia. *Am J Med.* 1985; 78:869-72.
32. HARRISON CN, CAMPBELL PJ, BUCK G, WHEATLEY K, EAST CL, BAREFORD D, WILKINS BS, VAN DER WALT JD, REILLY JT, GRIGG AP, REVELL P, WOODCOCK BE, GREEN AR; United Kingdom Medical Research Council Primary Thrombocythemia 1 Study. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia*. N Engl J Med*. 2005; 353:33-45.
33. RUZZON E, RANDI ML, TEZZA F, LUZZATTO G, SCANDELLARI R, FABRIS F. Leg ulcers in elderly on hydroxyurea: a single center experience in Ph- Myeloproliferative

disorders and review of literature. *Aging Clin Exp Res*. 2006; 18:187-90.
34. LATAGLIATA R, SPADEA A, CEDRONE M, DI GIANDOMENICO J, DE MURO M, VILLIVÀ N, BRECCIA M, ANACLERICO B, PORRINI R, SPIRITO F, RAGO A, AVVISATI G, ALIMENA G, MONTANARO M, ANDRIANI A; Gruppo laziale SMPC PH1 neg. Symptomatic mucocutaneous toxicity of hydroxyurea in Philadelphia chromosome-negative Myeloproliferative neoplasms: the Mister Hyde face of a safe drug. *Cancer*. 2012; 118:404-9.
35. ANTONIOLI E, GUGLIELMELLI P, PIERI L, FINAZZI M, RUMI E, MARTINELLI V, VIANELLI N, LUIGIA RANDI M, BERTOZZI I, DE STEFANO V, ZA T, ROSSI E, RUGGERI M, ELLI E, CACCIOLA R, CACCIOLA E, POGLIANI E, RODEGHIERO F, BACCARANI M, PASSAMONTI F, FINAZZI G, RAMBALDI A, BOSI A, CAZZOLA M, BARBUI T, VANNUCCHI AM; AGIMM investigators. Hydroxyurea-related toxicity in 3,411 patients with Ph'-negative MPN. *Am J Hematol*. 2012 May; 87:552-4.
36. MONTEFUSCO E, ALIMENA G, GASTALDI R, CARLESIMO OA, VALESINI G, MANDELLI F. Unusual dermatologic toxicity of long-term therapy with hydroxyurea in chronic myelogenous leukemia. *Tumori.* 1986; 72: 317-321.
37. NAJEAN Y, RAIN JD. Treatment of polycythemia vera: the use of hydroxyurea and pipobroman in 292 patients under the age of 65 years. *Blood*. 1997 1; 90: 3370-7.
38. RAIN JD. Hydroxyurea--is it a harmless drug in Vaquez disease?. *Pathol Biol (Paris).* 2001; 49:158-63.
39. MARTÍNEZ-TRILLOS A, GAYA A, MAFFIOLI M, ARELLANO-RODRIGO E, CALVO X, DÍAZ-BEYÁ M, CERVANTES F. Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: results in 40 patients. *Ann Hematol*. 2010; 89:1233-7.
40. OLESEN LH, PEDERSEN BB. [Hydroxyurea-induced leg ulcers in patients with chronic myeloproliferative disorders]. *Ugeskr Laeger*. 163 (2001) 6908-11 (Ab-stract)
41. SALMON-EHR V, LEBORGNE G, VILQUE JP, POTRON G, BERNARD P. Secondary cutaneous effects of hydroxyurea: prospective study of 26 patients from a dermatologic consultation. *Rev Med Interne*. 2000; 21: 30-34.
42. VASSALLO C, PASSAMONTI F, MERANTE S, ARDIGÒ M, NOLLI G, MANGIACAVALLI S, BORRONI G. Muco-cutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. *Clin Exp Dermatol*. 26 (2001) 141-8
43. BAROSI G, BIRGEGARD G, FINAZZI G, GRIESSHAMMER M, HARRISON C, HASSELBALCH H, KILADIJAN JJ, LENGFELDER E, MESA R, MC MULLIN MF, PASSAMONTI F, REILLY JT, VANNUCCHI AM, BARBUI T. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol*. 2010; 148: 961-963.
44. KIKUCHI K, ARITA K, TATEISHI Y, ONOZAWA M, AKIYAMA M, SHIMIZU H. Recurrence of hydroxyurea-induced leg ulcer after discontinuation of treatment. *Acta Derm Venereol.* 2011; 91: 373-374.
45. NATARAJAN S, WILLIAMSON D, GREY J, HARDING KG, COOPER RA. Healing of an MRSA-colonized, hydroxyurea-induced leg ulcer with honey. *J Dermatolog Treat.* 2001; 12: 33-36.
46. AKINCI B, YESIL S, ATABEY A, ILGEZDI S. Hydroxyurea associated leg ulcer succesfully treated with hyperbaric oxygen in a diabetic patient. *Exp Clin Endocrinol Diabetes*. 2007; 115:143-145.
47. YOUNG HS, KHAN AS, KENDRA JR, COULSON IH. The cutaneous side-effects of hydroxyurea. *Clin Lab Haematol.* 2000; 22: 229-232.
48. DACEY MJ, CALLEN JP. Hydroxyurea-induced dermatomyositis-like eruption. *J Am*

Acad Dermatol. 2003; 48: 439-441.
49. BURNS DA, SARKANY I, GAYLARDE P. Effects of hydroxyurea therapy on normal skin: a case report. *Clin Exp Dermatol.* 1980; 5: 447-449.
50. DISSEMOND J, HOEFT D, KNAB J, FRANCKSON T, KROGER K, GOOS M. Leg ulcer in a patient associated with hydroxyurea therapy*. Int J Dermatol*. 2006; 45:158-160.
51. HANCHI I, ZEGLAOUI F, EZZINE N, DAOUD L, KAROUI M, FAZAA B, RIDHA KAMOUN M. Leg ulcer in a patient treated with hydroxyurea for polycythemia vera. *Presse Med*. 2006; 35:1174-1176.
52. WEINLICH G, SCHULER G, GREIL R, KOFLER H, FRITSCH P. Leg ulcers associated with long-term hydroxyurea therapy*. J Am Acad Dermatol*.1998; 39:372-374.
53. HWANG SW, HONG SK, KIM SH, SEO JK, LEE D, SUNG HS. A Hydroxyurea-induced Leg Ulcer. *Ann Dermatol*. 2009; 21:39-41.
54. VÉLEZ A,GARCÍA-ARANDA JM, MORENO JC Hydroxyurea-induced leg ulcers: is macroerythrocytosis a pathogenic factor? *J Eur Acad Dermatol Venereol.*1999; 12: 243-244.
55. ENGSTRÖM KG, LÖFVENBERG E. Treatment of myeloproliferative disorders with hydroxyurea: effects on red blood cell geometry and deformability. *Blood* 1998; 91: 3986-3991.
56. VARMA S, LANIGAN SW. Dermatomyositis-like eruption and leg ulceration caused by hydroxyurea in a patient with psoriasis. *Clin Exp Dermatol*. 1999; 24:164-166. Jain 2005
57. JAIN V, GUPTA K, NAGPAL N. Perimalleolar ulcers in hydroxyurea treated patients with concomitant chronic venous disease: diagnostic pitfalls. J *Coll Physicians Surg Pak.* 2005; 15:658-60.
58. GOERGE T, SCHELLONG G, MESTERS RM, BERDEL WE. Mimicry of hydroxyurea-induced leg ulcer by distal vena saphena parva insufficiency. *Ann Hematol.* 2012; 91:471-2.
59. MCLINTOCK C, OCKELFORD PA. Hydroxyurea induced skin ulceration in myeloproliferative disorders. *Aust N Z J Med*. 2000;30:373-6.
60. FRANÇA ER, TEIXEIRA MA, MATIAS KDE F, ANTUNES DE, BRAZ RDE A, SILVA CE. Cutaneous effects after prolongaded use of hydroxyurea in Polycythemia Vera. *An Bras Dermatol.* 2011; 86:751-754.
61. POROS A, NÁDASDY K. Leg ulcer in hydroxyurea-treated patients. *Haematologia (Budap).* 2000; 30:313-8.
62. YOKOTA K, TASAKA T, IWATA K, OGAWA H, NAKANO M, SEKI K, OGURA S. Huge postoperative ulcer following hydroxyurea therapy in a patient with polycythemiavera. *Haematologica*. 2003; 88: ECR36.
63. STONE T, BERGER A, BLUMBERG S, O'NEILL D, ROSS F, MCMEEKING A, CHEN W, PASTAR I. A multidisciplinary team approach to hydroxyurea-associated chronic wound with squamous cell carcinoma*. Int Wound J.* 2012; 9:324-9.
64. K. HARTMANN, S. NAGEL, T. ERICHSEN, E. RABE, K. H. GRIPS, T. BIEBER, F. PANNIER-FISCHER. Cutaneous ulcers following hydroxyurea therapy. *Phlebologie* 33 (2004) 202–5
65. KENNEDY BJ. Hydroxyurea-associated leg ulceration. *Ann Intern Med*. 129 (1998) 252
66. NGUYEN TV, MARGOLIS DJ. Hydroxyurea and lower leg ulcers. *Cutis*. 1993; 52:217-9
67. DISSEMOND J, HOEFT D, KNAB J, FRANCKSON T, KROGER K, GOOS M. Leg ulcer in a patient associated with hydroxyurea therapy*. Int J Dermatol*. 2006; 45:158-

160.
68. KIDO M, TAGO O, FUJIWARA H, ITO M, NIWANO H. Leg ulcer associated with hydroxyurea treatment in a patient with chronic myelogenous leukaemia: successful treatment with prostagladin E1 and pentoxifylline. *Br J Dermatol*. 1998; 139: 1124-1126.
69. STAGNO F, GUGLIELMO P, CONSOLI U, FIUMARA P, RUSSO M, GIUSTOLISI R. Successful healing of hydroxyurea-related leg ulcers with topical granulocyte-macrophage colony-stimulating factor. *Blood.* 1999;94:1479-80.
70. FLORES F, EAGLSTEIN WA, KIRSNER RS. Hydroxyurea-induced leg ulcers treated with Apligraf. *Ann Intern Med*. 132 (2000) 417-8
71. ARAGANE Y, OKAMOTO T, YAJIMA A, ISOGAI R, KAWADA A, TEZUKA T. Hydroxyurea-induced foot ulcer successfully treated with a topical basic fibroblast growth factor product. *Br J Dermatol.* 2003; 148: 599-600
72. TSUCHIYA S, ICHIOKA S, SEKIYA N. Hydroxyurea-induced foot ulcer in a case of es-sential thrombocythaemia. *J Wound Care*. 19 (2010) 361-4
73. ROMANELLI M, DINI V, ROMANELLI P. Hydroxyurea-induced leg ulcers treated with a protease-modulating matrix. *Arch Dermatol*. 2007; 143:1310-1313.
74. MARTORELL-CALATAYUD A, REQUENA C, NAGORE-ENGUÍDANOS E, GUILLÉN-BARONA C. Multiple, painful, treatment-resistant leg ulcers associated with dermatomyositis-like lesions over the interphalangeal joints induced by hydroxyurea. *Actas Dermosifiliogr*. 2009;100:804-7.
75. FIORAMONTI P, FINO P, PARISI P, SCUDERI N, ONESTI MG. A case of hydroxyurea-induced leg ulcer after definitive treatment suspension in a patient affected by thrombocythemia: effectiveness of a new collagenase. *In Vivo*. 2012; 26:1053-6.
76. KATO N, KIMURA K, YASUKAWA K, YOSHIDA K. Hydroxyurea-related leg ulcers in a patient with chronic myelogenous leukemia: a case report and review of the literature. *J Dermatol*. 1999; 26:56-62.
77. FRANCIS S, BAREFORD D, BAGGOTT C, THACHIL J. Prognostic implications of leg ulcers from hydroxycarbamide therapy in patients with essential thrombocythaemia. *Leuk Res*. 2012; 36:488-90.
78. BRAWLEY OW, CORNELIUS LJ, EDWARDS LR, GAMBLE VN, GREEN BL, INTURRISI C, JAMES AH, LARAQUE D, MENDEZ M, MONTOYA CJ, POLLOCK BH, ROBINSON L, SCHOLNIK AP, SCHORI M. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. *Ann Intern Med*. 2008; 148:932-8.
79. CHAINE B, NEONATO MG, GIROT R, ARACTINGI S. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. *Arch Dermatol*. 2001; 137: 467- 470.
80. NZOUAKOU R, BACHIR D, LAVAUD A, HABIBI A, LEE K, LIONNET F, HULIN A, JOUAULT H, PRÉHU C, ROUDOT-THORAVAL F, GIROT R, GALACTÉROS F. Clinical follow-up of hydroxyurea-treated adults with sickle cell disease. *Acta Haematol*. 2011; 125:145-52.
81. KERSGARD C, OSSWALD MB. Hydroxyurea and sickle cell leg ulcers. *Am J Hematol*. 68 (2001) 215-6
82. BADAHDAH H, SNYDER R, O'CONNOR C, NASSIER W, KARBASIAN Z, ABADEER M. Mixed etiology hydroxyurea-related lower leg ulcer that masqueraded as sequelae from sickle cell disease and venous insufficiency, *Wounds*, 2012; 24:254–257
83. LANZKRON S, STROUSE JJ, WILSON R, BEACH MC, HAYWOOD C, PARK H, WITKOP C, BASSEB, SEGAL JB. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. *Ann Intern Med*. 2008; 148:939-955.
84. LADIZINSKI B, BAZAKAS A, MISTRY N, ALAVI A, SIBBALD RG, SALCIDO R. Sickle cell

disease and leg ulcers. *Adv Skin Wound Care*. 2012; 25:420-8.

Figure 1 Dermatologic adverse effects of hydroxyurea

A: Ulcer in the ankle area in a patient with chronic myelogenous leukemia under treatment with HU. Notice the melanonychia affecting the first toe.

B: Longitudinal band of the toenail after prolonged HU administration.

Figure 2 Hydroxyurea induced ulcer

Ulcer on the lateral aspect of the lower leg in a 76-year-old female patient affected by essential thrombocythemia after 3 years of HU-treatment.

Figure 3 Hydroxyurea-induced ulcers: pathogenetic factors

Multiple factors are involved in the genesis of HU-induced ulcers. Minor traumas, such as the contact with shoes in the malleolar region, act as trigger of the ulcer. Because of HU cytostatic effect, basal epidermal cells don't have the regenerative potential to repair the lesion. HU-induced macrocytosis impairs blood flow in the microcirculation and cause relative ischemia in the basal regenerating layer of the skin. Patients affected by MPDs are usually old and therefore vascular insufficiency and diabetes, well-known risk factors for ulcers, are common. HU: hydroxyurea

Figure 4: Algorithm for the diagnosis and treatment of Hydroxyurea-induced leg ulcers.

Cutaneous ulcers associated with hydroxyurea therapy: a comprehensive review

Table 1. Mucocutaneous side effects of hydroxyurea

1. Skin atrophy , xerosis cutis, and acquired ichthyosis,.
2. Facial and acral erythema,
3. Palmoplantar keratoderma
4. Alopecia
5. Cutaneous and mucosal hyperpigmentation
6. Dermatomyositis-like eruptions
7. Onychodystrophy, and melanonychia
8. Actinic keratoses and squamous cell carcinomas
9. Cutaneous and mucosal ulcers

Cutaneous ulcers associated with hydroxyurea therapy: a comprehensive review

Table 2. Anamnestic, clinical and instrumental findings relevant to the diagnosis of HU-induced ulcer.

1. Present or past long term and high dose treatment with HU.
2. History of interferon α therapy.
3. History of minor trauma in the site of lesion.
4. History of previous ulcers during HU treatment.
5. Presence of painful, multiple, bilateral, recidivating ulcer usually in the perimalleolar area.
6. Presence of other form of HU mucocutaneous toxicity (See Table 1)
7. Presence of macrocytosis.

HU, hydroxyurea

Cutaneous ulcers associated with hydroxyurea therapy: a comprehensive review

Table 3. Possible histopathologic findings in hydroxyurea-induced ulcers

1. Leukocytoclastic vasculitis
2. Lymphocytic infiltration
3. Formation of thrombi
4. Thickening of vessel walls
5. Dermal fibrosis
6. Hyperkeratosis

Table 4. Published advanced therapies in the management of hydroxyurea-induced drugs

Therapy	Mechanism of action	Outcome
Dextranomer dressing (31)	Cicatrizant effect	1 patient recovered 1 patient improved
Prostaglandins E1 and I2 (44,68)	Vasodilatation	1 patient recovered in 1 month 1 patient recovered in 4 months
Topical Granulocyte-Macrophage Colony-Stimulating Factor (69)	Recruitment and proliferation of monocytes and macrophages modulating cytokine production	3 patients recovered in 2 weeks 1 patient recovered in 1 month
Human skin equivalent (63,70)	Skin substitution	1 patient recovered in 3 weeks 1 patient improved
Manuka honey and hydrocolloid dressing (45)	Antibacterial activity	1 patient recovered in 3 weeks
Topical basic fibroblast growth factor (71,72)	Angiogenic activity	1 patient recovered in 2 weeks 1 patient showed no improvement
Bovine collagen sponge or powder (73,74)	Protease-modulating agents	2 patients recovered in 2 months 1 patient improved
Sodium hyaluronate and bacterial collagenase (75)	Enzymatic debridement	1 patient recovered in 3 months

Cutaneous ulcers associated with hydroxyurea therapy: a comprehensive review

Table 5. Preventive strategies in HU induced ulcer management

1. Avoid, if other treatment is possible, HU treatment in patients with high risk factors for ulcer development.
2. Inform the patients and their relatives about the mucocutaneous toxicity of HU-treatment and advice immediate medical alert in case of suspected lesions.
3. In high-risk patients, suggest opportune leg protections and solar filters.
4. Patients should undergo regular dermatologic evaluations, especially after long term treatment.
5. A cardiovascular check-up could be advised in patients who developed ulcer after HU-treatment

HU, hydroxyurea

Figure 1a

Click here to download high resolution image

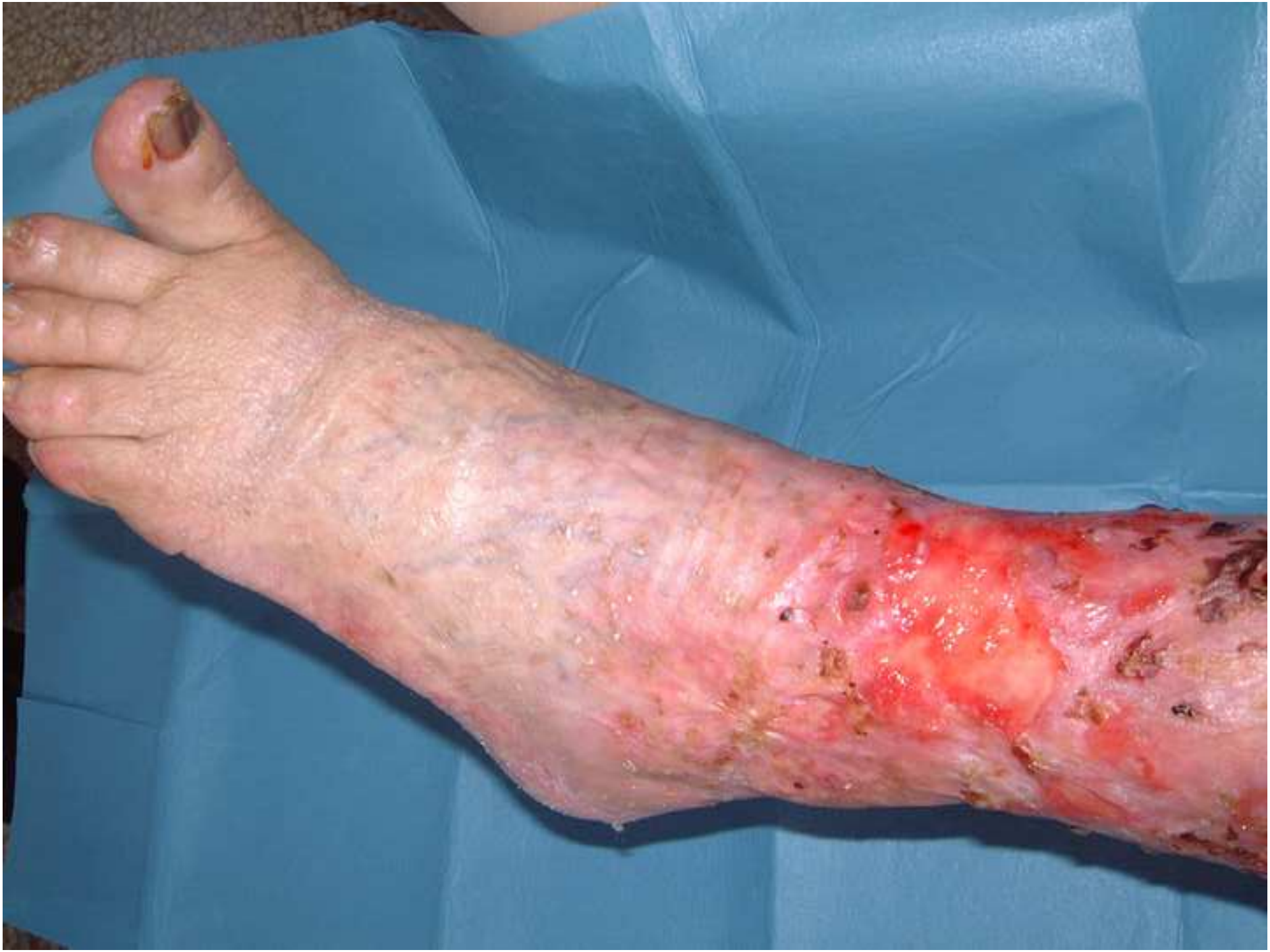

Figure 1b

Click here to download high resolution image

Figure 2

Click here to download high resolution image

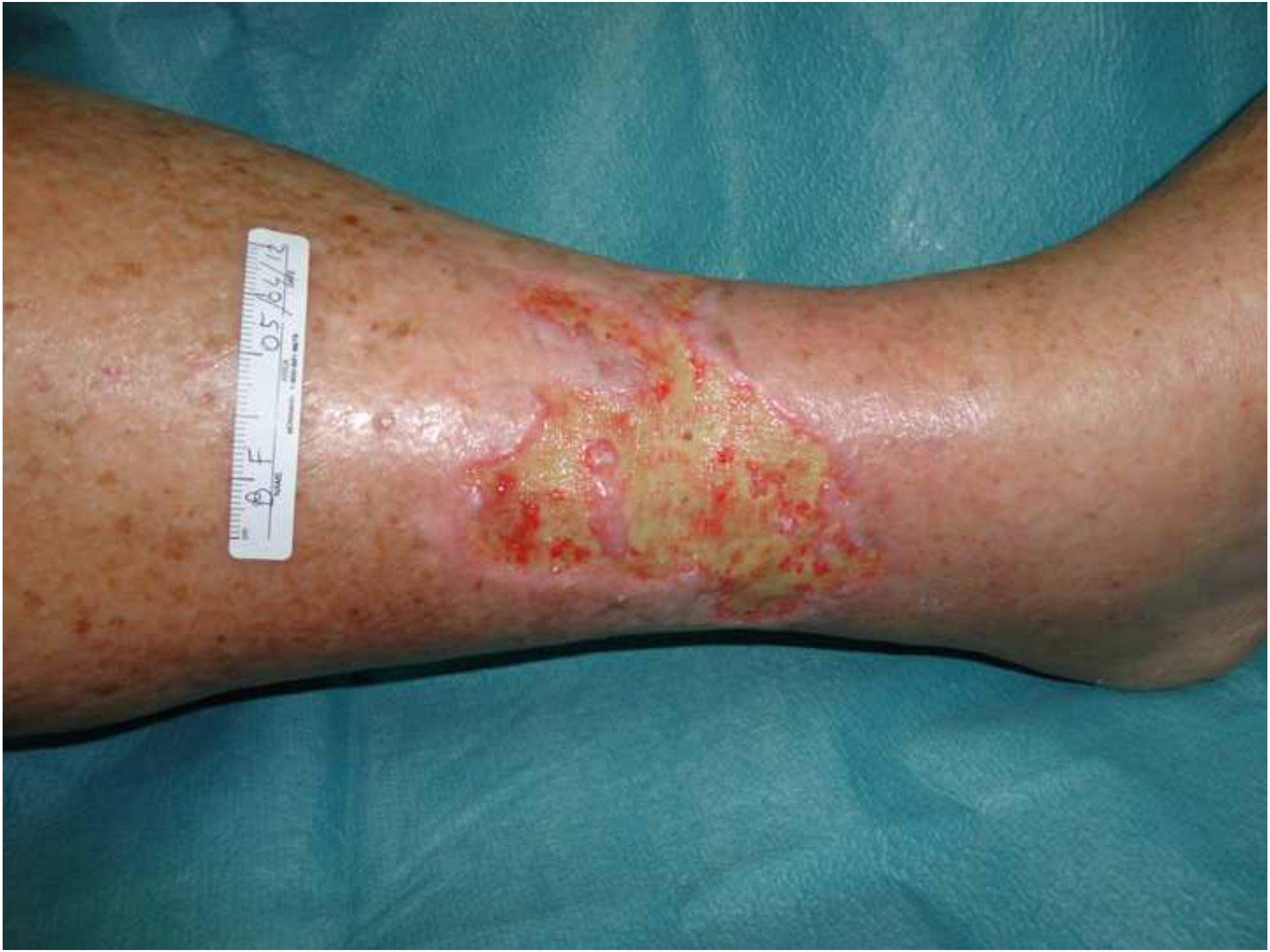

Figure 3

Click here to download high resolution image

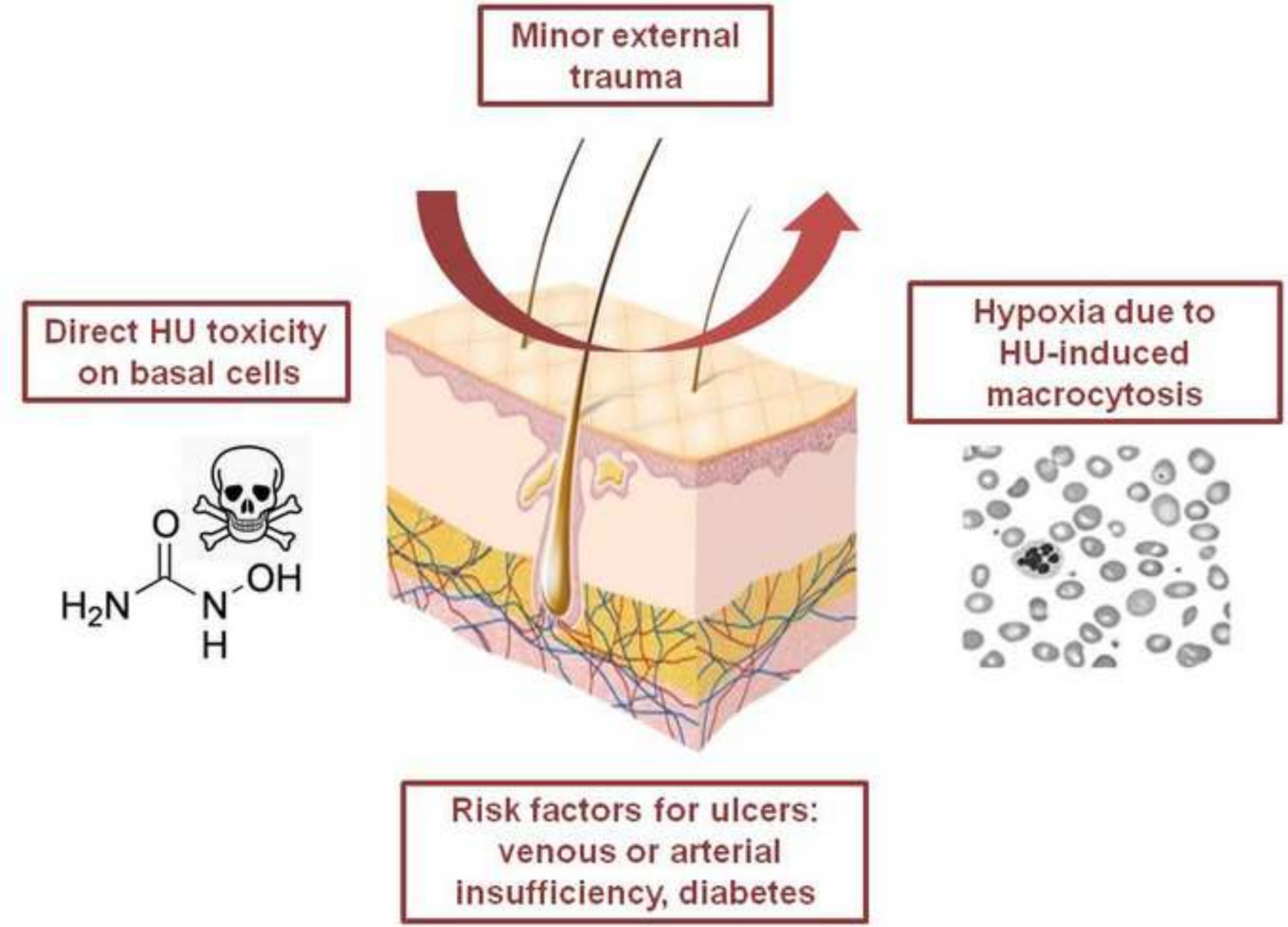

Figure 4

Click here to download high resolution image