Treatment of a chronic skin lesion in the lower limb in Meleda disease

Abstract: Chronic venous skin lesions heal quickly with compression therapy and wound bed preparation. However, there are conditions in which the tissue repair process is more difficult, such as Meleda disease. Meleda disease is a rare genetic pathology, transmitted with an autosomal recessive gene with a prevalence of 1:100 000; it is also called palmoplantar keratoderma. In this pathology, there is a state of chronic inflammation, an alteration of the extracellular matrix and migration of fibroblasts and keratinocytes, which block the proliferative phase of the tissue repair process. Through targeted interventions and the use of bioactive dressings, it is possible to heal the venous ulcer, although this can take a long time. The authors report their experience in relation to a patient with Meleda disease and venous ulceration of seven years.
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chronic skin lesion • genetic mutations • Meleda disease • palmoplantar keratoderma • tissue repair • wound

Meleda disease is a rare genetic pathology, which is transmitted by an autosomal recessive gene, and has a prevalence of 1:100 000. It is also called palmoplantar keratoderma.

Characterised by palmoplantar hyperkeratosis, it involves the palms of the hands and soles of the feet, extending to the dorsal part of the hands as well as the wrists and heels.

The disease takes its name from the first case described in patients on the island of Meleda in Croatia.[1] In 1930, Bosnjakovic and Kogoj described nine cases of this pathology, six women and three men.

Several forms of palmoplantar keratoderma are described in the literature.

Diffuse epidermolytic palmoplantar keratoderma (also known as palmoplantar keratoderma cum degeneratione granulosa Vörner), a disease that occurs in the first months of life, is characterised by a symmetrical, well-defined thickening of the palms of the hands and soles of the feet.

Diffuse, non-epidermolytic, palmoplantar keratoderma (also known as keratosis extremitatum progrediens) is inherited as an autosomal dominant condition and is present from childhood. It is characterised by a well-defined, symmetrical, often waxy keratoderma that involves the entire palms of the hands and soles of the feet.

Meleda pathology occurs in the first years of life with hyperkeratosis and acanthosis. Over the years, it tends to get progressively more severe and disabling, with the possible appearance of psoriasiform lesions at the knees and elbows, and skin infections related to the increase in the bacterial load of the skin. Skin thickening can lead to functional limitations in the joints.

The genetic mutation is located on chromosome 8q24.3, within a group of homologous human genes Ly-6 with mutation in the ARS B gene, coding for SLURP-1 (secreted Ly-6/UPAR-related protein 1).[2]

The SLURP-1 protein can bind to nicotinic acetylcholine receptors (nAChR) in the skin and, through interaction with these receptors, it interferes in the control of growth and division (proliferation) and maturation (differentiation) of skin cells. Changing SLURP-1 would increase the secretion by macrophages of tumour necrosis factor (TNF)-α, a pleiotropic factor engaged in inflammatory responses.[3]

In the case described here, the patient, in addition to the typical manifestations of Meleda disease, had a chronic skin lesion at the medial malleolus of the left lower limb dating from seven years.

Presentation and treatment protocol

The patient, a man aged 84 with Meleda disease, was first observed by the authors in February 2020. He had a chronic skin injury to the lower third of the left limb that had started over the medial malleolus (Figs 1–4).

The lesion had a fibrinous wound bed, with perilesional erythema associated with palmoplantar hyperkeratosis. An echo-colour Doppler highlighted saphenopopliteal superficial venous insufficiency and ectasia of the suprafascial veins.

Previously, the lesion had been cleaned with saline, followed by the application of collagenase to the wound bed, sterile gauze and an unspecified bandage.

Our therapeutic protocol had the following steps:

- Cleansing the periwound skin and the lesion with surfactant detergents based on polyhexanide-biguanide. This was to:
  - Remove contaminants

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Fig 1. Palmoplantar hyperkeratosis in Meleda disease on hands of the patient in case study

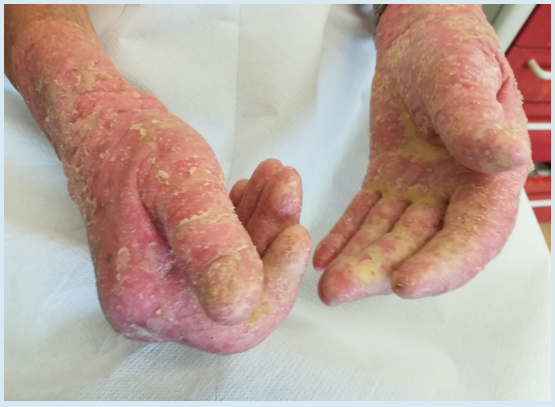


Fig 2. Palmoplantar hyperkeratosis extended to dorsal aspect of hand of patient in case study

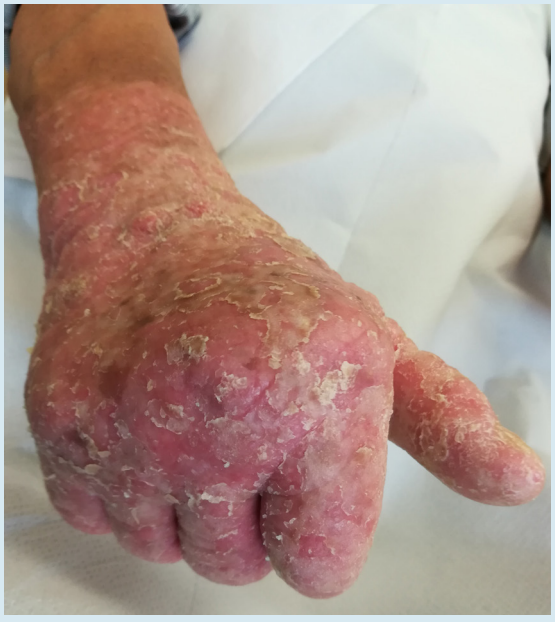


Fig 3. Lower leg of patient in the case study, showing hyperkeratosis extended to dorsal aspect of the foot

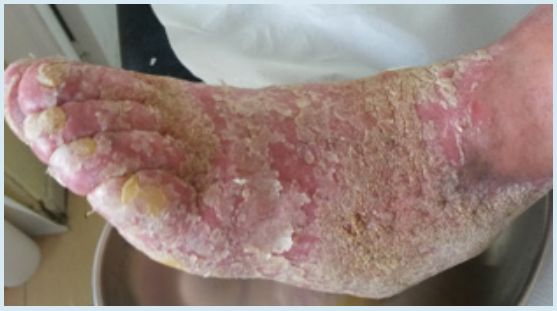
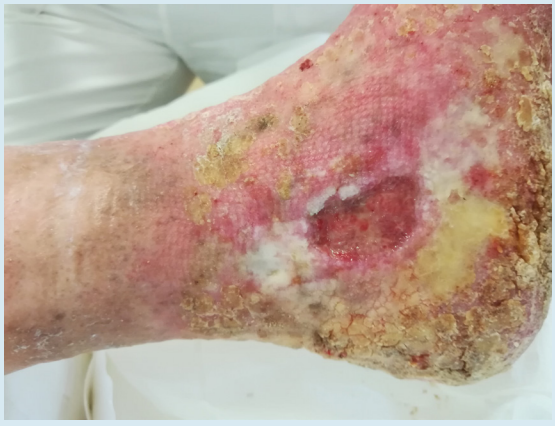


Fig 4. Chronic skin lesion at the medial malleolus of the left lower limb of patient in case study



- Remove any residue of previous medication
- Remove microorganisms from the wound bed
- Reduce bacterial biofilm
- Remove periwound hyperkeratosis
- Remove excess secretions and ensure patient comfort

- Debridement of the lesion and the periwound margins, using a sterile disposable swab soaked in polyhexanide and betaine
- Application of collagenase on the wound bed to eliminate collagen fibres to facilitate the loss of necrotic material, which impedes tissue repair
- Application of periwound zinc oxide to protect the margins of the lesion
- Applying a lipocolloid dressing and urea-based cream to the surrounding skin and areas with hyperkeratosis
- Compression therapy with short-stretch bandaging.

During this phase, the patient was treated every day.

Once the fibrin on the base of the lesion had been removed, enzymatic debridement was stopped and a dressing containing glycosaminoglycans was applied to the lesion below a lipocolloid dressing. The application of a multi-component bandage, including a short-stretch bandage, completed the therapeutic protocol. In this phase, the patient was treated every four days.

The patient gave approval for publication of his details, including photographs.

Results

The application of the above protocol led to the disappearance of fibrinous material (slough) in the lesion after a few weeks. However, despite compression therapy—the cornerstone of venous ulcer therapy—the lesion did not heal.

The application of substances that stimulate cell proliferation on the bed of the lesion, based on glycosaminoglycans, combined with compression, allowed the wound to heal after 5 months of treatment (Figs 5–6).

Fig 5. Skin lesion applied with substances that stimulate cell proliferation

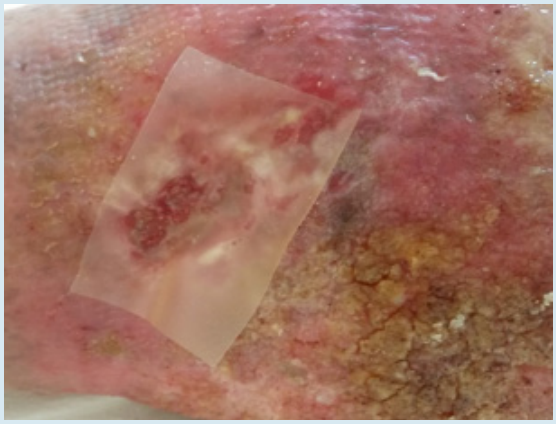


Fig 6. Skin lesion at the end of the treatment

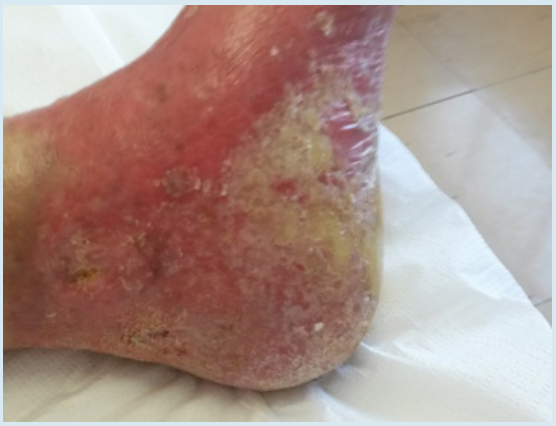
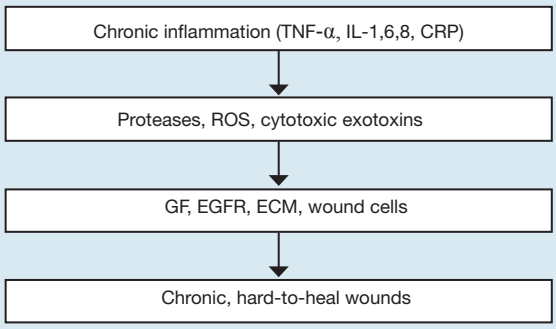


Fig 7. Development of hard-to-heal wounds



CRP—C-reactive protein; ECM—extracellar matrix; EGFR—epidermal growth factor receptor; GF—growth factor; IL—interleukin; ROS—reactive oxygen species

Discussion

The tissue repair process is somewhat complex, and is divided into stages of haemostasis/inflammation, proliferation and remodelling. During these phases, numerous cellular elements (e.g., platelets, leucocytes and fibroblasts) and molecules (e.g., growth factors, interleukins, proteoglycans and glycomesoglycans) intervene to initiate and complete wound healing.

In chronic skin lesions, the tissue repair process stops at the inflammatory phase, not passing on to the proliferation and remodelling stages. The possible blocking factors can be: local (e.g., high bacterial load and biofilm formation, the presence of non-viable tissue and excessive exudate) and systemic (e.g., immunodeficiencies, the use of immunosuppressant drugs and vascular disease).

In prolonged inflammation, the persistence of high levels of pro-inflammatory cytokines called matrix metalloproteases (MMPs) destroys the extracellular matrix and blocks growth factors; in addition, high levels of TNF-α reduce the levels of platelet-derived growth factor that are necessary for cell proliferation (Fig 7).

Furthermore, a possible increase in bacterial load leads to an increase in metabolic consumption, an increase in oxygen consumption and tissue ischaemia.

The presence of bacteria must be considered not only within the lesion but also on the periwound skin. Bacterial species forming biofilms can further hold back the tissue repair process.

The extracellular matrix (ECM), a structural scaffold on which fibroblasts are organised, is composed of two classes of macromolecules: glycosaminoglycans and fibrous proteins. The former include hyaluronic acid, chondroitin sulphate, heparan sulphate, heparin and dermatan sulphate. The latter comprise two groups: collagen and elastin, which have mainly structural functions; and fibronectin, laminin, entactin and vitronectin, whose function is adhesive.

ECM is the substrate on which all tissue cells can adhere, migrate, proliferate and differentiate, influencing their survival, form and function.

The ECM macromolecules sequester growth factors and molecules such as water or minerals. They also control physiological phenomena such as morphogenesis, pathophysiological phenomena such as wound healing and pathological phenomena such as invasion and metastasisation.

In a patient with Meleda disease, many factors capable of blocking the healing process coexist and are related to genetic mutations linked to the protein SLURP-1.

This mutation changes keratinocyte apoptosis, with:

- Inflammation of the epidermis and dermis and perivascular lymphocyte infiltrate[4]
- An increase in the levels of TNF-α pro-inflammatory cytokine, blocking the repair process in the inflammatory phase
- Functional anomalies of urokinase-type plasminogen activator (also known as urokinase), which increases the degradation of the ECM
- Increased bacterial load present on the periwound skin linked to skin thickening from hyperkeratosis and hyperhidrosis.

Through the above, our treatment protocol aimed to modulate each possible factor responsible for blocking the tissue repair mechanism and followed the principles of wound bed preparation.[5]

During the entire treatment cycle, a solution of polyhexanide and betaine was used to cleanse the lesion and periwound skin. This was done to control bacterial load and biofilms; mechanical debridement was carried out with a device made up of a front microfibre layer, for effective removal of debris, backed by an absorbent polypropylene layer.[6]

Cleansing and debridement are the first steps in the management of lesions, as the presence of non-vital tissue (such as dry eschar, fibrin and slough) hinders healing by offering an optimal microenvironment for the growth of microorganisms; this can cause a progressive increase in the bacterial load until it reaches states of critical colonisation, biofilm formation and infection.[7]

The wound margin and periwound skin need to be protected to promote wound healing. Perilesional skin is the area of skin that extends for 10cm beyond the margin of the lesion and it requires care to maintain barrier integrity, conserve the hydrolipidic film and support the newly formed epithelium.

This process follows the TIME process: tissue debridement, infection or inflammation, moisture balance and edge effect.[8]

In Meleda disease, hyperkeratosis and chronic inflammation decrease cell migration and ECM deposition.[8] To protect the margin and periwound skin, a 20% zinc oxide cream was applied to the margin and periwound skin, and a 20% urea-based cream was applied to the skin beyond the periwound area.

The ECM facilitates the repair of the skin wound through: direct modulation of cellular processes such as adhesion, migration, proliferation and cell differentiation; and indirect regulation of the secretion and activation of the extracellular protease or of the activity of the growth factors necessary for migration of inflammatory cells, fibroblasts, keratinocytes and endothelial precursor cells to the wound site.[9]

Recent studies have provided insights into the significant relationship between cell migration during wound repair and glycosaminoglycans, mainly as ECM components, but also because they can regulate the release of cytokines and the activity of growth factors.[10]

Because of changes in the ECM in chronic skin lesions, which are even greater in Meleda disease, once the non-viable tissue had been removed from the wound, a dressing consisting of mesoglycan was applied. This contained chondroitin sulphate, dermatan sulphate, heparan sulphate and heparin.

The rationale of this treatment is based on the product's ability to induce a significant cytoskeletal reorganisation given by an increase in the formation of stress fibres from F-actin. This increases the cell migration rate of fibroblasts and keratinocytes. In particular, fibroblasts display a notable change in shape and orientation.

The dressing, consisting of mesoglycan (Prisma Skin), a substance that stimulates cell proliferation, induces the formation of new vessels by endothelial cells (neoangiogenesis) and longer capillary structures with a large number of branches. The mesoglycan dressing leads the cells to the endothelial–mesenchymal transition, suggesting the transition to a fibroblast-like phenotype, as demonstrated by immunofluorescence tests. There is also inhibition of inflammatory reactions such as nitric oxide secretion and nuclear translocation of NF-κB into endothelial cells and the production of TNF by macrophages.[11]

Because of the venous insufficiency in the patient, a multi-layered, multi-component bandage consisting of zinc oxide bandage and short-stretch adhesive bandage was applied.

Conclusion

The management of chronic skin lesions with venous aetiology in general is not particularly difficult, as long as the underlying cause is corrected, venous hypertension is addressed and the lesion is approached following the principles of wound bed preparation and the TIME approach.

The situation is different when systemic and/or local factors block the wound healing process.

In the patient with Meleda disease, a rare genetic pathology, several elements hinder the process of tissue repair, prolonging the inflammatory phase and hindering the proliferative one.

In particular, the marked increases in MMPs and TNF, the structural anomalies of the ECM, the delay in migration of fibroblasts and epithelial cells from the perilesional margin and hyperkeratosis make healing difficult.

To achieve wound healing, it was necessary to apply, in addition to the classic principles of wound bed preparation, a series of interventions aimed at modifying the local conditions of the pathology **JWC**

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Reflective questions

- Can you think of any genetic diseases that prevent ulcers from healing? And if so, how?
- Is the wound bed preparation approach different in chronic skin lesions that are aggravated by hereditary diseases?
- How are biostimulants and dressings that control metalloproteases useful in non-healing lesions?

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