Photodynamic therapy—a promising treatment option for autoimmune skin ulcers: a case report

Stefania Motta* and Marcello Monti

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We describe a 38-year-old woman with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) who developed two symmetric paramalleolar ulcers with similar diameters, depths and borders, that were successfully treated with photodynamic therapy with 5-aminolevulinic acid (ALA-PDT).

Case report

A 38-year-old woman was brought to our attention in October 2004 because of painful and progressive ankle ulcers. She had been previously diagnosed as having systemic lupus erythematosus (SLE) in 1990 and antiphospholipid syndrome (APS) in 2002, with predominantly skin involvement consisting of livedoid-like vasculitis and photosensitivity, and had been treated with steroids. She was receiving mycophenolate but had developed painful, symmetric malleolar ulcers that were recalcitrant to a prostacyclin analogue and systemic antibiotics associated with various topical wound dressings. The ulcers had a diameter of 4 cm (on the right ankle) and 3.8 cm (on the left), were punched out, and had a fibrinotic bed and surrounding erythema; they were extremely painful (visual analogue scale, VAS: 5–8) but showed no clinical signs of infection.[1] Tissue from both ulcers was cultured for microrganisms and found to be contaminated by S. aureus (methicillin sensitive). Because of the failure of previous treatments ALA-PDT was proposed.

With the patient's formal informed consent, we treated the left ulcer with a dressing only and the right ulcer with a dressing and ALA-PDT. Both ulcers were cleaned twice a day with a solution of benzalkonium chloride 0.2%, dressed with hydrophilic ointment containing allantoin (MOST PEG ointment by MOST Technical Cosmetics, Milan, Italy) and covered with cotton gauze kept in place by elastic nets. The right ulcer was also treated once a week with 10% ALA in PEG ointment applied in occlusion for 2 h and then exposed to diode red light at 630 nm, irradiance 160 mW at 50 mm (S 630, AlphaStrumenti, Milan, Italy) for eight minutes delivering 75 J cm^{-2}. Fluorescence was detected using visible violet light at 405 nm and, after ALA application, was specifically localised on the epidermis surrounding the border of the ulcer (Fig. 1). Pain intensity was assessed by means of VAS, with values of 3–5 being recorded for both ulcers throughout the period of treatment.

After six weeks, the PDT-treated ulcer was less painful than the other and had shrunk to a diameter of 1.8 cm, whereas the left ulcer still had a diameter of 3.2 cm. ALA-PDT was well tolerated, with the patient experiencing minimal discomfort.

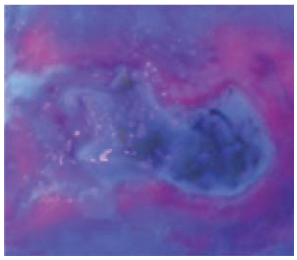

Fig. 1 Representative example of protoporphyrin IX fluorescence of ulcer-surrounding skin after application of ALA (the picture was taken from a patient similar to the case under discussion).

The patient subsequently asked to have both ulcers treated with PDT and, after a further six weeks, the right ulcer had healed and the left had shrunk to a diameter of 0.8 cm (Fig. 2). Both ulcers healed within three months leaving depressed white scars, and have not recurred since. No adverse cutaneous or systemic effects due to ALA were reported.

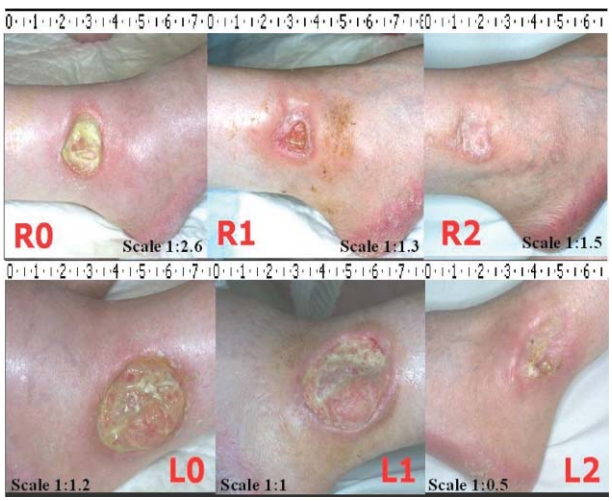

Fig. 2 R0. Right ulcer at admission; R1. Right ulcer after 6 ALA-PDT applications; R2. Right ulcer after 12 ALA-PDT applications. L0. Left ulcer at admission; L1. Left ulcer after 6-week dressing; L2. Left ulcer after 6 ALA-PDT applications.

Discussion

It is thought that skin ulcers in SLE are caused by specific vascular damage intrinsic to the disease and are also a consequence of immunesuppressant treatment. Both factors slow healing

Università degli Studi di Milano and Istituto Clinico Humanitas, Via Manzoni 56, 20089, Rozzano, Milan, Italy. E-mail: stefania.motta@humanitas.it; Fax: +390282244693; Tel: +390282244050

processes and promote bacterial overgrowth, and so SLE ulcers are challenging to treat. Our patient's ulcers healed after three months of weekly ALA-PDT treatment.

A number of *in vitro* and animal studies have shown the healing potential of PDT, but there are few data concerning humans, although Clayton *et al*.[2] have reported the successful use of ALA-PDT in one case of infected leg ulcers. Given our patient's systemic disease and the status of the ulcers after the failure of previous treatments, and despite the therapy the patient was receiving (mycophenolate), it is likely that ALA-PDT treatment had healing effects. In accordance with the design of our procedure, the ALA-PDT treated ulcer healed whereas the ulcer treated with a dressing alone only decreased in size (16%).

The mechanisms of action of ALA-PDT in ulcer closure are still unknown, but at least four non-exclusive hypotheses are possible: (a) marginal keratinocyte photoactivation, (b) anti-inflammatory action, (c) immunomodulatory activity and (d) antimicrobial activity. There is increasing evidence that the epidermis has important metabolic, endocrine and immunological functions that are brought about by the secretion of various mediators including cytokines, and that keratinocytes are a major source of interleukins and transforming growth factors. On the basis of the results of recent studies,[3] it seems that PDT triggers matrix metalloproteinase production in fibroblasts by means of an indirect paracrine loop mediated by keratinocyte-released soluble factors. As topical ALA-PDT primarily targets border keratinocytes (Fig. 1), it is likely that epidermal cytokines can modulate nearby keratinocytes by means of an autocrine pathway, and influence other cell types by means of paracrine mechanism.

In skin areas treated with ALA-PDT, inflammatory reactions seem to slow down because of the death of resident macrophages and mast cells and of the slow recovery to cytokine responsiveness of the surviving cell population.

When ALA-PDT is used to treat acne vulgaris, it reduces inflammatory acne lesions,[4] and so it is possible that it may also reduce inflammation by modulating the network of pro- and anti-inflammatory mediators.[5]

It is generally accepted that PDT causes acute inflammation, but it is also thought that the judicious application of acute inflammation can interrupt the process of chronic inflammation and stimulate healing.

PDT can not only activate but also suppress the immune response depending on several variables; it acts as a biological response modifier.[6]

In addition, an antimicrobial activity has been demonstrated for PDT with porphyrins[7] that might be clinically useful.

Although studies have shown porphyrin activity, especially on Gram+ strains, indirect evidence suggests broad spectrum activity. However, more data are needed to demonstrate this clinical finding by means of antimicrobial control of ALA-PDT on the proliferation of bacteria in the ulcer bed.

Despite the fact that ALA was repeatedly applied to the open wounds of our SLE-APS patient, there were no systemic effects. This is important because, although she was extremely sensitive to solar light, she did not experience any increased photosensitivity or any clinical worsening during her exposure to ALA and 630 nm red light. This observation underlines the difference between the cell damage caused by UV light (which mainly affects DNA) and that caused by ALA-PDT, which mainly involves mitochondria.

Our case demonstrates the favourable activity of ALA-PDT in skin ulcer closure in comparison with a standard dressing, and allows us to suggest ALA-PDT as a valid alternative strategy for the control of ulcers caused by systemic vascular and immunological processes.

Although further studies are necessary to elucidate the mechanisms of action of ALA-PDT in treatment of chronic skin ulcers, our experience suggests that PDT may play a role in wound healing.

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