



Scar Symptom: Erythema and Thickness

Yating Yang, Xiaoli Wu, and Wei Liu

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Definition

Erythema is derived from the Greek *erythros*, which refers to the redness of skin or mucous membrane. Erythema is common in pathological scars (hypertrophic scar and keloid) and premature physiological scars where inflammation-induced angiogenesis and capillary dilation are mostly responsible. Different from the temporary and self-relieving redness in normal skin caused by allergy or mechanical friction (such as massage), the existence and severity of erythema in scar tissues are consistent with their maturity and inflammation state inside, serving as a convenient monitor of scar quality and treatment response. Scar thickness indirectly reflects the extent of scar development by collagen deposition.

11.1 Mechanisms of Erythema in Scar

In general, the common causes of erythema can be roughly categorized into four groups: inflammation, mechanical stimulation (massage, waxing, and tweezing of hairs), radiation (sunburn, radiotherapy), allergies and other chemical agents. Despite the pervasive nature of erythema in both physiological and pathological scars, the development mechanisms remain to be relatively less explored and therefore limited effective treatment options are available. However, previous studies demonstrated that inflammation, vascularization, and sometimes epidermis defect are the three major mechanisms that contribute to the erythema in scars.

11.1.1 Inflammation-Induced Capillary Perfusion Is Crucial for Erythema Initiation

Accumulated studies have confirmed that the inflammation induced by various reasons (infection, foreign body, immune dysfunction, etc.) is greatly associated with the formation of scars, especially hypertrophic scars and keloids [1]. Stimulated by inflammatory cytokines, capillaries constrict to increase the local blood flow and vessel permeability, resulting in erythema and sometimes elevated skin temperature [2]. It was shown that significant increase of blood flow values was detected in erythematous scars when compared to healthy skin [3, 4]. Besides, erythema (measured by colorimetry) is often interpreted as an indirect measurement of the blood flow in clinical practice as it indicates the hyperemia in superficial capillaries. Bae-Harboe *et al.* first introduced the term “postinflammatory erythema” (PIE) in 2013 to describe erythema often seen after the resolution of

inflammatory acne or other inflammatory skin conditions [5]. To be specific, the symptom of erythema persists all along the inflammatory stage of wound healing and plays multiple roles in this process.

11.1.2 Vascularization Dynamically Participates in the Erythema Development

The chronic inflammatory stimulation and hyperproliferation of scar tissues deteriorate the local hypoxia and promote the secretion of angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (BFGF), and hypoxia-induced factor 1 (HIF-1) [2, 6]. As reported by Amadeu *et al.*, hypertrophic scars contain an increased number of dilated vessels in papillary and reticular dermis compared to normal skin [7]. The increased capillary density and dilated vessel diameter then contribute to the formation of erythema, in line with the study of Fullerton, who stated that erythema is determined by the blood volume under a given area, and not by the product of erythrocyte velocity and concentration [8]. Clinically, erythema disappears on finger pressure (blanching), which also suggests that the vascular remodeling is involved.

Scar erythema, blood flow, microvessels, and redness are four features of scar that are often interchangeably used under the item “vascularization” or “vascularity.” However, by directly measuring erythema with colorimetry, blood flow with laser Doppler imaging (LDI), vessels with immunohistochemistry, and subjective scale of redness with POSAS, respectively, Jaspers *et al.* found only significant relevance between erythema and subjective redness, but no correlations between the others. In contrast, Mermans *et al.* found that erythema was associated with blood flow, but this correlation was not consistent at different test moments [9]. Moreover, Kischer *et al.* reported that most microvessels were occluded in hypertrophic scars due to an excessive number of endothelial cells [10, 11]. And the higher hematocrit and the enlarged vessels would then result in a more sluggish blood velocity and lower blood flow values. Taken together, it is now understood that the term “vascularity” describes a dynamic process, and the four criteria mentioned above can attribute to the redness either independently or interact with each other at different stages of scar development. These exploration studies express well the complexity of erythema formation and enlighten us to view this process dynamically instead of simply putting them under the umbrella of “vascularization,” especially in clinical practice.

11.1.3 Thinner Epidermis Is Directly Responsible for the Transparency in Erythematous Scars with Skin Barrier Defect

The epidermal thickness and collagen synthesis are directly associated with the transparency of skin. Oliveira *et al.* and Busch *et al.* identified a thinned-out skin texture in burn scar that makes the intense circulation of blood becoming more apparent [3, 12]. They argued that increased skin redness is not only considered as an inflammatory symptom but also the structural modification of subdermal components. And the induction of percutaneous collagen (IPC) and angiogenesis therapies (medical needling and fractional laser) has been proven to be effective to adjust the skin color after repetitive treatments [12].

Different from the thinner epidermis in physiological scars resulting from normal wound-healing process, keloids and hypertrophic scars are characterized by extra collagen deposition and increased epidermal thickness [13]. But recent studies also hypothesized a skin barrier defect in keloid scars, which may possibly alter the opacity of epidermis [14].

11.2 Contributions of Erythema to Scar Development and Associated Clinical Symptoms

The wound-healing process contains three chronological but partially overlapped phases: inflammatory stage (day 1–6), proliferation stage (day 4–week 3), and remodeling stage (week 3–1 year). Parallel with this process, Van Der Wal *et al.* reported that the erythema index scores of scars reduce significantly within 12 months [15] as a result of the common pathological mechanisms they shared. To be specific, the alleviation and deterioration of erythema are closely associated with the scar development since they indirectly reflect the inflammatory state and angiogenic activity beneath the skin. And since the redness of erythema (from pink to scarlet to purple) is the result of different proportion of hemoglobin (the red oxygenated state, absorbed at 660 nm) and deoxyhemoglobin (dark red, absorbed at 940 nm) in the capillaries of the dermis, the color of scarred skin can serve as a monitor of local hypoxia, angiogenesis, and microcirculation.

Although the most commonly used principles for measuring scar color are narrow-band reflectance spectrophotometry and tristimulus reflectance colorimetry

[4], researchers found statistically significant correlation between erythema values (colorimetry) and subjective redness assessment (Patient and Observer Scar Assessment Scale, POSAS) ($r = 0.403$, $p = 0.030$) [4], proving the reliability of subjective erythema measurement in clinical practice.

Similarly, erythematous scars are more likely to suffer from pain or pruritus as a result of inflammatory stimulation and suspicious vulnerability of scar fibroblasts (previous studies detected an elevation of α -adrenoreceptors expression on keloid fibroblasts and predicted that it might be related to paresthesia in scar tissues [16]).

Elevated temperature is directly associated with overperfusion of vessels especially arteries in deeper layer of the skin [4] and is not common in thickened scar tissues, but the existence of which could be explained as a sign of infection or active inflammatory state.

Generally, erythema reflects the inflammation and angiogenesis activity, as well as structural remodeling of scar tissues to serve as a monitor of scar maturation and quality. Since patients and clinicians often determine the success of treatment by the visual appearance of a scar, erythema measured by POSAS could be an accessible method to evaluate the treatment response and help to set the endpoint for the course.

11.3 Scar Erythema and Scar Thickness

There is no direct relation between scar erythema and scar thickness, because the former reflects the level of inflammation and angiogenesis process, whereas the latter indicates the extent of cell proliferation and extracellular matrix production and deposition. Such phenomenon has been frequently observed in clinical practice that a highly inflamed scar with severe erythema might be thin and soft in texture, whereas a dark-colored keloid could be thick and abundant with collagen. However, enhanced erythema by strong angiogenesis provides nutrition for fibroblast proliferation and matrix production, and therefore reducing erythema also helps to prevent scar thickening.

11.4 Clinical Measurement of Scar Redness and Thickness

Colorimetric plate along with photography is the conventional methodology to semi-objectively measure the redness of scars. Doppler ultrasound can detect blood flow inside a scar, but it reflects activity in a relatively deep blood vessel. For superficial blood flow inside the

surface capillaries, laser speckle might be the technique to quantitatively measure the erythema change.

Manual measurement is the conventional way to assess scar thickness. With advances in technology, ultrasound and nuclear magnetic resonance can quantitatively provide data of scar thickness. In addition, 3D scanner not only provides the gross view of a thick scar, but also provides quantitative data of scar thickness and volume.

11.5 Clinical Relevance

11.5.1 Clinical Treatment Strategies of Erythema in Scars

Traditional clinical treatments of erythema in scar tissues mainly target on anti-inflammation and anti-proliferation, such as topical glucocorticoid and compression garments. The spreading applications of laser treatments and medical needling provide therapists with powerful arms that can interfere with erythema formation from various perspectives. Besides, systematic elements including imbalanced diets, stressful lifestyles, and even genetic predisposition may also be responsible.

11.5.1.1 Anti-inflammation Strategies to Alleviate Erythema and Hinder Scars Development

Inflammation is one of the major risk factors of both scar development and erythema. Since corticoid can effectively reduce the production of pro-inflammatory mediators and inhibit inflammatory processes in the dermis, the intralesional triamcinolone acetonide (TCA) injection has been widely used alone or as an adjuvant therapy to treat hypertrophic scars and keloids [17]. Besides, although the application of triamcinolone tapes is limited by its penetrating ability, it can be stuck to the scar area and release the drug all day long. Moreover, clinical studies observed a better performance of triamcinolone when combined with 5-Fluorouracil [17]. Other topical anti-inflammation treatment such as silicone gel sheeting that increases the elasticity of burn scar tissue also showed a reduction in pruritus, erythema, and scar thickness [18]. Systematic glucocorticoid application is not recommended for risks of complications such as diabetes, infections, and Cushing's syndrome.

11.5.1.2 Laser Treatments to Interfere with Erythema from Multiple Perspective

Laser therapy is one of the most widely used methods to treat erythema in scars. Ablative fractional lasers that create columns of vaporized tissue with surround-

ing eschar and coagulated tissue can improve various features of burn scars including erythema. Kawecki *et al.* observed that 31% of hypertrophic burn scar patients had resolution of erythema with resulting normal skin tone after ablative fractional laser treatment [19]. Coagulating microvessels with the selective photothermolysis of wavelengths around 595 nm, pulsed dye laser (PDL) can decrease inflammation and edema in erythematous scars and shows satisfactory outcomes in color repair. Similarly, Q-switched Nd:YAG lasers with a wavelength of 1064 nm in very short pulses are promising solutions to superficial angiogenesis of erythematous skin, especially in decreasing the vascular prominence in PIE [17, 18, 20]. Studies have demonstrated minimal side effects including atrophic scarring (0.8%), hyperpigmentation (1%), hypopigmentation (2.6%), and dermatitis (2%), among 500 patients treated with PDL [21]. Notably, although PDL and Nd:YAG have shown good results in reducing the red color of scars, skin erythema itself is one common adverse effect of laser treatment, which suggests that the laser therapy should be carefully selected and be practiced with cautions especially in patients with a history of post-treatment erythema or scar constitution.

11.5.1.3 Compression Therapy

Compression therapy (or occlusive dressings) has been widely applied to hypertrophic scar patients as a first-line agent with good results in decreasing erythema, thickness, and hardness of burn scars [22, 23]. A total of 60% of patients treated with compression devices showed 75–100% enhancement in scar condition according to previous studies [17]. The anti-scar effects of occlusive garments are thought to be related to occlusion and hydration [7, 17]. Some literature reported that this change is likely because of the inhibition of transforming growth factor (TGF)- β 1 release and ultimately decreased fibroblast activity [24].

11.5.1.4 Medical Needling

Although sounding contradictory, the bleeding process of medical needling can influence vascularization by stimulating angiogenesis in the post-wound healing cascade and improve the vital thickness of the epidermis (directly related to skin transparency) by inducing percutaneous collagen synthesis.

Based on the outcomes of objective measurements, medical needling achieves a normalization of the skin color and an adjustment to healthy skin after repetitive treatments [12], and it has clinically shown to improve the abnormal vascular proliferation that occurs in PIE. Similarly, fractional resurfacing lasers have been used to induce structural remodeling and skin regeneration.

11.6 Clinical Treatment for Thick Scar

Contracture and functional disability caused by hypertrophic scars need surgical interventions. As for thick keloids, surgical therapy is also preferred. In addition, intralesional injection with 5-fluorouracil and steroid, cryotherapy, pressure therapy, and radiotherapy are all potential therapeutic options for thick scars, and these will be introduced in various chapters of this book and thus will not be the focus of this chapter.

11.7 Conclusion

The scar erythema is a burden for patients, as it amplifies the cosmetic problems and is associated with other unpleasant feelings such as pain and itching. Moreover, the development of erythema parallels with the dynamic process of inflammation, angiogenesis, scar formation, and thickening. Although most studies consider erythema as a concomitant byproduct following wound healing, it also promotes scar development via enhancing angiogenesis to provide scar fibroblasts essential nutrition for collagen production and deposition, and thus it has become an important therapeutic target as well. Although many issues remain to be explored such as what determines erythema presence, persistence, and disappearance, the erythema/redness itself can serve as a visible symptom reflecting treatment response and thus help both patients and therapists to set a relevant endpoint.

Take-Home Messages

Both erythema and thickness are key characteristics of scar, which can be used to monitor scar development and therapy efficacy. Angiogenesis represented by scar redness is a key contributor to pathological scar development due to enhanced inflammation, which can also serve as an important therapeutic target.

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