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Highlighting the rim of the perifollicular epidermal unit

The perifollicular and interfollicular areas of normal skin may look similar. However, some physiological and pathological processes may specifically involve a thin perifollicular rim. This review illustrates some of the methods available for highlighting the rim of the perifollicular epidermal unit. Non invasive methods rely on dermoscopy, ultraviolet light enhanced visualization (ULEV), skin capacitance imaging and cyanoacrylate skin surface strippings (CSSS). Conventional histology and immunohistochemistry may also show specific perifollicular features without, however, revealing the aspects highlighted by the specific non invasive methods. The clinically relevant modifications consist of pigmentary and hyperkeratotic perifollicular changes.

Key words: hair follicle, dermoscopy, ULEV method, melanoderma, cyanoacrylate skin surface stripping

At any given body site, the structure of the epithelium may look uniform in the clinical inspection of the normal-looking skin. However, the site of hair follicle openings should probably be considered as a peculiar area exhibiting differences from the interfollicular area [1-3]. Indeed, some physiological and pathological features specifically manifest themselves in the perifollicular area. Skin biopsy is part of routine dermatological practice. Standard histology and immuno-histochemistry represent the time-honoured methods for documenting perifollicular disorders. However, some physiological characteristics are not readily visualized on histological sections, and may require specific non-invasive physical methods to be disclosed and documented.
Physiological manifestations restricted to the perifollicular area on white skin consist of the speckled perifollicular subclinical melanoderma [1, 3, 4]. Follicular lichen planus, follicular psoriasis, seborrheic dermatitis, follicular keratosis, pityriasis rubra pilaris and incipient graft-versus-host disease are examples of diseases presenting alterations of the perifollicular area [5, 6]. Many other dermatoses, particularly in darker skinned people, can show peculiar perifollicular changes [7]. In addition to close clinical examination, some complementary methods can highlight these changes which are keratotic or pigmented in nature. This review focuses on these methods, particularly on non-invasive procedures. Due to the distinct and specific optical and non-optical skin properties explored by these methods, it is obvious that some aspects can be detected by some instruments and not by others.

Dermoscopy

Dermoscopy is a convenient means for recording any perifollicular hyperkeratosis *(figure 1)*. These changes are usually best seen in darker skin types because the contrast between the whitish hyperkeratosis and the normal surrounding skin is increased.

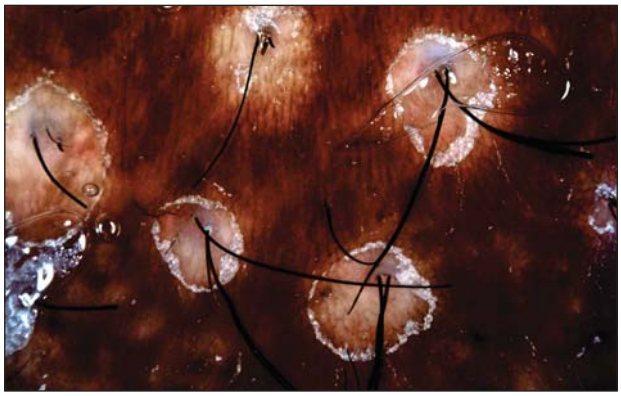

Figure 1. Perifollicular psoriasis on darker skin (dermoscopy, × 42).

Some pathophysiological variations in the pigmentation of the perifollicular area can also be seen by dermoscopy. The contrast between the perifollicular and the interfollicular areas is usually better appreciated in people of darker complexion. The most common patterns are macular hypermelanosis *(figure 2A)*, annular hypermelanosis *(figure 2B)*, macular hypomelanosis (*figure 2C)* and targetoid leucomelanoderma *(figure 2D)*.

ULEV method

The ultraviolet light-enhanced visualization (ULEV) method is a convenient tool for highlighting discrete or even subclinical xerotic [8, 9] and pigmentary changes [1, 3, 4, 10]. ULEV can be performed using a computer-assisted video camera equipped with an internal UV-emitting unit (Visioscan® VC98, C+K Electronic, Cologne, Germany). The camera must be closely applied to the skin

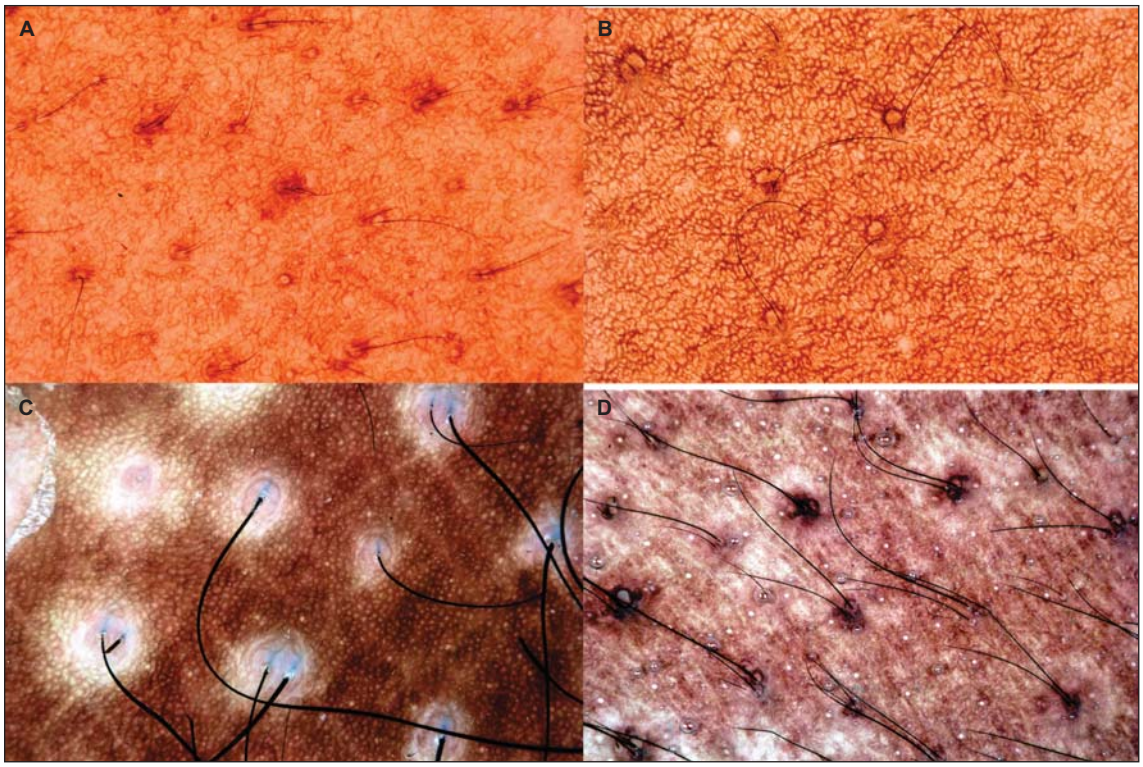

Figure 2. Pigmentary perifollicular changes (dermoscopy, × 42). **A)** macular perifollicular hypermelanosis, **B)** annular perifollicular hypermelanosis, **C)** macular perifollicular hypomelanosis, **D)** targetoid perifollicular leucomelanoderma.

surface. The digital signal generated corresponds to 256 grey levels, ranging from zero for black to 256 for white. The subclinical mottled pigmentation of the skin can be thus recorded. The perifollicular spotty subclinical melanoderma is one of the patterns of mosaic hyperpigmentation *(figure 3A)*. The relative area of these darker spots can be computerized. It is noteworthy that these spots exhibit a regular rounded aspect centered by a follicular opening.

The same method can illustrate the effect of a keratolytic agent. The first visible effect consists of lifting of a desquamating perifollicular rim *(figure 3B)*.

Skin capacitance imaging

Skin capacitance imaging is a novel application of the silicone image sensor (SIS) technology currently used for biometric fingerprint recognition [11-13]. The sensor measures multiple values of electrical capacitance over a given skin surface area. As such, it gives information about both the topography and the hydration of the skin surface. Skin capacitance imaging can conveniently be obtained using the SkinChip® device (L'Oréal, Paris) which contains 92160 capacitors located every 50 µm over a 18*12.8 mm

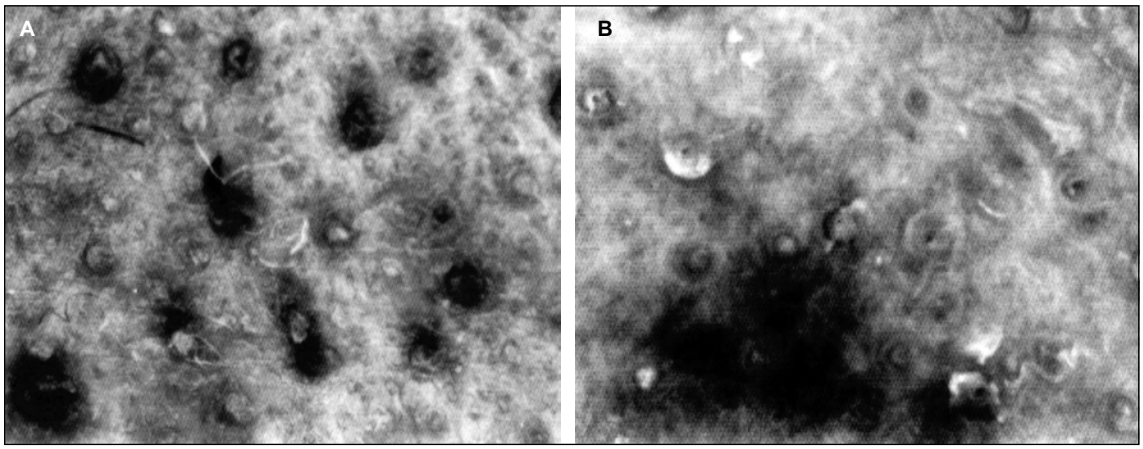

Figure 3. Subclinical perifollicular changes (ULEV method, × 25). **A)** perifollicular melanoderma, **B)** perifollicular desquamation induced by a β hydroxyacid.

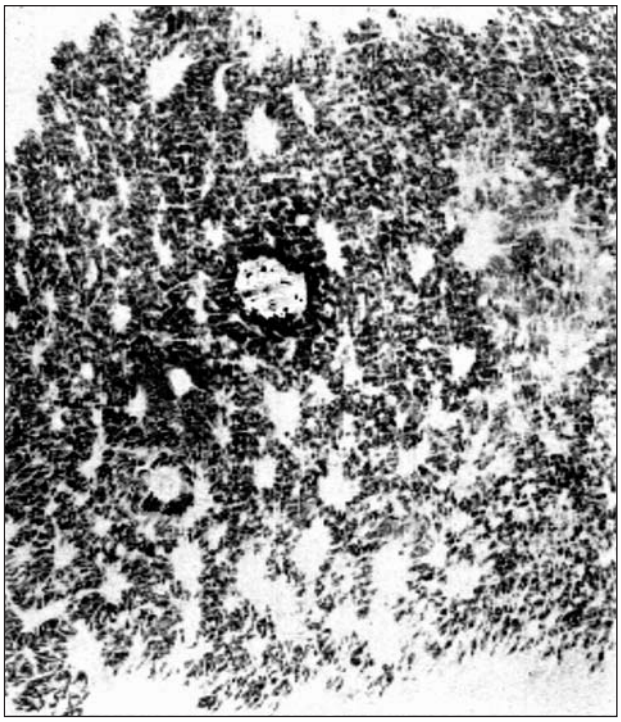

Figure 4. Skin capacitance imaging of acne. White dots corresponding to microcomedones and a larger targetoid inflammatory papule (× 4).

plate. The capacitance values are coded in a range of 255 grey levels by a specific image capture software, thus generating a capacitance map of the skin surface. Such skin capacitance imaging can reveal some functional aspects of the perifollicular area, particularly in acne lesions [14]. Micromedones appear as whitish dots of low capacitance *(figure 4)*. Acne papules are often centered by a larger white and rounded structure circled by a darker high capacitance rim corresponding to the erythematous inflammatory reaction.

Cyanoacrylate skin surface stripping

Cyanoacrylate skin surface strippings (CSSS) consist of harvesting the superficial part of the stratum corneum and any keratotic material inside the acroinfundibulum [3, 15-22]. The CSSS method was launched about 35 years ago and its use has been expanded and refined in time. A droplet of cyanoacrylate glue is deposited onto a glass slide or on a sheet of clear polyethylene (Melinex O, ICI plastic division). This material is pressed against the surface of the skin for at least 30 s. In the presence of moisture, the cyanoacrylate polymerizes and adheres to the stratum corneum. The material is gently lifted and peeled from the skin. Follicular casts and microcomedones may be conveniently sampled using CSSS *(figure 5A)*. The material collected from the upper portion of the follicular ducts reflects the balance between formation and lysis of comedones. A perifollicular rim of hyperkeratosis can also be seen *(figure 5B)*.
Analytical methods for evaluating the amount of follicular casts rely on image analysis when illuminating the specimen with white light, polarized light, or fluorescent light.

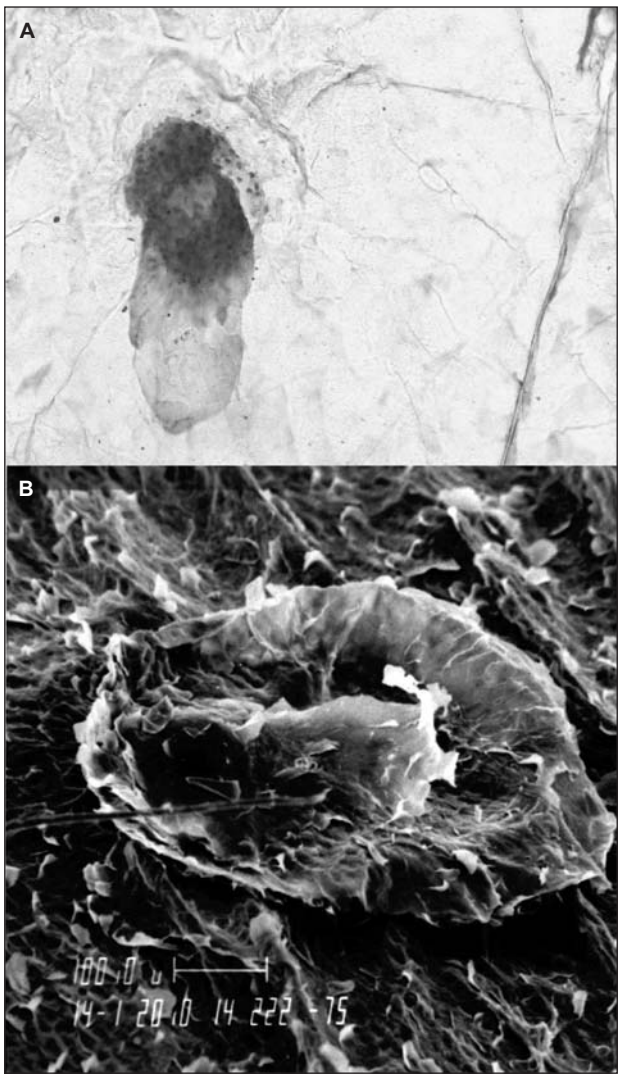

Figure 5. Follicular hyperkeratosis (cyanoacrylate skin surface biopsy). **A)** Parakeratotic follicular plug (Toluidine blue-basic fuschin stain, × 160). **B)** Follicular keratotic plug and perifollicular xerotic collaret (scanning electron microscopy, × 300).

The use of fluorescence for evaluating the presence of porphyrins produced by *Propionibacterium acnes* in follicles may prove to be difficult to interpret in relation to concomitant application of drugs and cosmetics. In fact, some products emit fluorescence by themselves and others display a quenching effect by absorption of porphyrin fluorescence. Moreover, fluorescence is not always limited to comedones and stratum corneum creases may fluoresce as well.

Histology and immunohistochemistry

Histological sections of a skin biopsy can show specific changes in the vicinity of the hair follicle opening [2]. For instance, a parakeratotic rim at the lips of a follicular infundibulum is quite frequent in incipient seborrheic dermatitis *(figure 6)*.

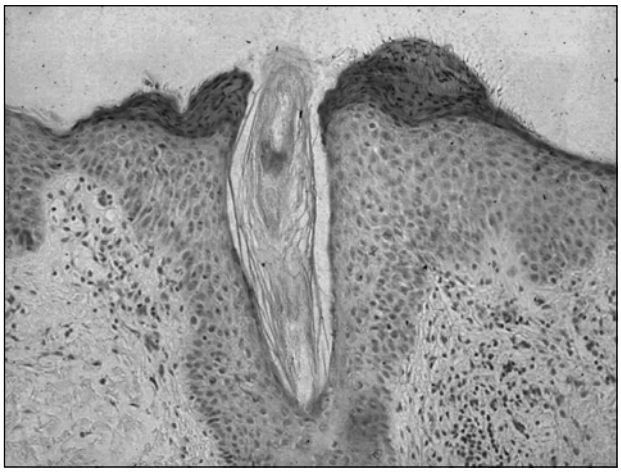

Figure 6. Perifollicular parakeratotic rim in seborrheic dermatitis (conventional histology, hematoxylin eosin stain 160 ×).

Immunohistochemistry can also highlight some specificities of the follicular and perifollicular epithelium. The positive calprotectin immunolabelling and the negative α5 (IV) collagen immunolabelling of the follicular epithelium and basement membrane, respectively, are useful to assess follicular differentiation [23, 24].

Histology *versus* biometrological methods

The above mentioned non-invasive methods are not substitutes for but additional tools to histology. The fields where some correlation may be found are perifollicular hyperkeratosis and pigmentary changes.
Perifollicular hyperkeratosis is indeed visible on histological slides. Dermoscopy, skin capacitance imaging, CSSS and the ULEV method can also show the same changes. However, the pictures provided by these non invasive methods explore a large area parallel to the skin surface, contrasting with the minute surface field revealed by histological sections cut perpendicularly to the skin surface. CSSS, as an optical method, provides information about the cell nature (corneocyte, parakeratotic cell) similar to histology. Dermoscopy, skin capacitance imaging and the ULEV method do not identify the cells, but rather inform about the severity of the hyperkeratotic process.
The subtle variations in the melanin pigmentation of the skin revealed by dermoscopy or the ULEV method are difficult or even impossible to perceive by histology. In other words, the sensitivity of dermoscopy and ULEV methods is much higher than that of conventional histology in detecting pigmentary variations.

Comments

The methods described here highlight specific aspects of the perifollicular area. The images given by the different tools allow distinct perceptions of the skin surface appearance and physical properties. The major expressions visible feature pigmentary differences and hyperkeratosis. These changes may remain subclinical or be revealed clinically.

As a rule, the bioengineering methods are much more sensitive than visual observation by clinicians. The invisible changes at routine examination may represent physiological characteristics unrelated to specific disorders. They may, however, be involved in the pathogenesis of peculiar follicular-centred diseases. Further studies would be welcome in order to unveil the relationship between the disclosed physiological changes and skin pathology.
Being aware of the structural and functional differences at the skin surface raises some doubts on the interpretations given to some global instrumental assessments, blurring the specific characteristics of the perifollicular epidermal unit. The unique aspects of the perifollicular epidermal unit may be due to intrinsic differences in the tissue structures. Other aspects may be secondary to various processes specifically occurring at the site of the infundibulum including the sebum load and microorganisms.
Mapping the differences of the skin characteristics using non-invasive optical and non-optical imaging can probably clarify better subtle clinical biological features. They help exploring "subclinical dermatology" by giving insight into skin physiology, early signs of skin disorders, treatment effects and dermocosmetology. ■

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