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The Pseudo-elongation of Capillaries in Psoriatic Plaques

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The intrapapillary vessels in the psoriatic plaque are described as elongated, twisted and multiplied. However there is neither proliferation nor necrosis of vessels in growing and dissolving psoriatic plaques. In 120 patients suffering from psoriasis vulgaris, computer-supported image analysis and in 8 patients additionally 3D reconstructions were made to investigate the regression process of the intrapapillary capillaries in the active and resolving psoriatic plaque. In acanthotic epidermis with a thickness of >400 μm the first subpapillary horizontally oriented plexus is included in the papilla due to the down-growing of the epidermal rete pegs. In the evaluation of the computer-supported image analysis there is only little variation in the levels of the different vascular plexuses within the dermis, while the epidermis is decreasing from >600 μm to >100 μm. In the 3D reconstruction of the transition of a psoriatic lesion into adjacent non-involved skin it could be proved that, apart from the epidermal alterations, there is virtually no difference in the arrangement of the vessels between the psoriatic lesion and the adjacent non-involved skin. In psoriasis the vessels do not proliferate, they rest as resident structures and are embraced by the down-growing rete pegs.

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So far, the function of the vascular system in the pathogenesis of psoriasis has remained speculative. The intrapapillary vessels in the psoriatic plaque seem elongated, twisted and multiplied (1, 2, 3, 4). This elongation and increased density of the capillaries could only be explained assuming blood vessel growth (2, 3, 5, 6). However, there are factors contradicting angiogenesis in psoriasis: first of all, no increase in endothelial cell proliferation in psoriatic lesions could be demonstrated; secondly, no decay products accumulate in the regression phase of a psoriatic plaque (6).

There is thus a discrepancy between the histological aspect of elongated multipled capillaries in the papillary region of a psoriatic lesion and the lack of proliferative processes of the vascular endothelia.

The subepidermal capillaries have to be viewed at their connection with the deeper situated vessels of the dermis. The dermal vessels are classified into several segments: from ascending arterioles the terminal arterioles, develop by arborizing within a superficial, horizontal plexus and from these arise the intrapapillary capillary loops. The venous limbs of the capillary venules evolve into postcapillary venules which form the venous network of the superficial vascular plexus. This plexus is connected to the subcutaneous venous system by the descending collecting venule (2, 7, 8, 9).

Using computer-supported three-dimensional reconstruction (10) and image analysis (11) we investigated the regression process of the intrapapillary capillaries in the active and resolving psoriatic plaque.

MATERIALS AND METHODS

Patients and biopsies

Punch biopsies were obtained from fully developed and resolving lesions of 120 patients with psoriasis vulgaris, in 10 cases additionally from adjacent, clinically normal skin. Table 1 shows the patient material and gives information about the biopsy sites.

Biopsies were fixed in formalin 5% for 12 h and embedded in paraffin wax. From 7 patients part of the tissue was also fixed in glutaraldehyde 3.5% and embedded in Epon 811.

Computer-supported image analytic evaluation (program analySIS®)

All 120 paraffin-embedded specimens were assessed by means of image analysis. From each biopsy at least 10 serial sections were obtained. Measurements were performed at 2 different locations on the 7 μm thick paraffin sections, 6 distances were measured each.

In this study we evaluated the following parameters (Fig. 1).

Parameters measured

epmax = epidermal thickness from the bottom of the rete pegs to the top of the granular layer
epmin = epidermal thickness from the top of the papillae to the top of the granular layer
pap = distance between basement membrane beneath epmin and the loop of the intrapapillary capillary
pl 1 = distance between the basement membrane below epmax and the first subpapillary, horizontally oriented plexus
pl 2 = distance between the basement membrane below epmax and the second subpapillary, horizontally oriented vascular plexus
pl 3 = distance between the basement membrane below epmax and the third horizontally oriented vascular plexus in the deep dermis

Table I. *Patients and biopsy sites assessed by means of computer-supported image analytic evaluation, program analySIS®*

Sex	*n*	forearm	upper arm	lower leg	thigh	back	abdomen	head	hand	armpit
Males	74	32	16	9	2	15	2	3	1	2
Females	46	16	10	7	1	12	2	1	1	0

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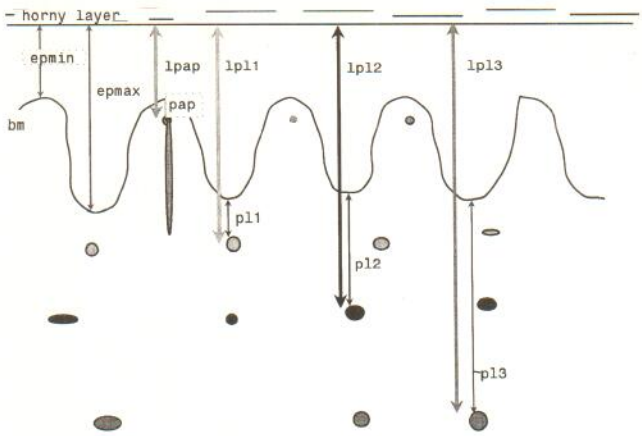

Fig. 1. Measured and calculated parameters evaluated by image analysis.

Calculated parameters

lpl 1 = epmax + pl 1 = level of pl 1 in the dermis (distance of pl 1 to skin surface)
lpl 2 = epmax + pl 2 = level of pl 2 in the dermis (distance of pl 2 to skin surface)
lpl 3 = epmax + pl 3 = level of pl 3 in the dermis (distance of pl 3 to skin surface)
lpap = epmin + pap = level of pap in the dermis (distance of the intrapapillary capillary loop to skin surface).

Specimens were evaluated at magnification of ×40 and ×250 under a Laboval (Zeiss) light microscope equipped with a CD-camera connected to an IP-8/AT matrox frame grabber board within an IBM-compatible 486 PC/AT. We used the image analysis program analySIS®, Soft-Imaging Software GmbH, Münster, Germany. The above-mentioned parameters (e.g. epmax, epmin, etc) were assessed by manual outlining of the structures of interest (using the mouse) on the digitalized microscopic image displayed on the monitor. Calibration of the video input channel in analySIS® allowed us to measure all distances in their actual length in micrometres.

To determine the exact location of the horizontally running vascular plexuses, the vessels were followed up over the whole length of the specimens; frequently, additional controls in adjacent serial sections were necessary (7).

In each specimen, too different measurements of each distance were obtained.

The measured values were further processed and displayed in graphs using the program Excel and MS-Windows®.

All measured values were sorted with regard to eprnax in descending order. Groups were formed with epmax ≥ 600 μm (group 1), ≥ 500 μm (group 2), ≥ 400 μm (group 3), ≥ 300 μm (group 4), ≥ 200 μm (group 5) and ≥ 100 μm (group 6).

For every group the mean value and standard deviation (δ) of all parameters were determined.

The mean values of the parameters of each group are presented in line diagrams.

Table II. *Patients sorted with regard to epmax*

group 1 = epmax ≥ 600 μm
group 2 = epmax ≥ 500 μm
group 3 = epmax ≥ 400 μm
group 4 = epmax ≥ 300 μm
group 5 = epmax ≥ 200 μm
group 6 = epmax ≥ 100 μm

Group	epmax	n	m	f
1	> = 600	4	2	2
2	> = 500	5	3	2
3	> = 400	18	12	6
4	> = 300	28	16	12
5	> = 200	34	23	11
6	> = 100	31	18	13

Computer-supported 3-dimensional reconstruction

Using the program 3D SIS, we 3-dimensionally reconstructed in 8 patients the vessels in the fully developed and resolving psoriatic plaques by evaluation of serial sections. Apart from the vessels, the stratum corneum and the basement membrane were also demonstrated.

In 1 patient we reconstructed the subepidermal vessels and the epidermis at the border of a psoriatic plaque, using serially cut 7 μm paraffin sections (transition of lesional skin into adjacent, clinically normal skin).

Results

Image analytic evaluation

In the fully developed psoriatic plaques the mean values of epmax range from 646 μm (δ = 27, 22) (group 1) to 437 μm (δ = 20) (group 3). During healing, epmax decreases to 150 μm (δ 28). Epmin shows, independent of epmax, a constant value of about 70 μm (Fig. 2). Table II gives information about biopsy-sites in the different groups.

Lpl 1, lpl 2 and lpl 3 are reduced with decreasing epmax (Fig. 3). During healing of the psoriatic plaque pl 1, pl 2 and pl 3 change levels in the dermis:

When epmax is higher than 500 μm, lpl 1 is on average 800 μm, which means that the first subpapillary, horizontally ori-

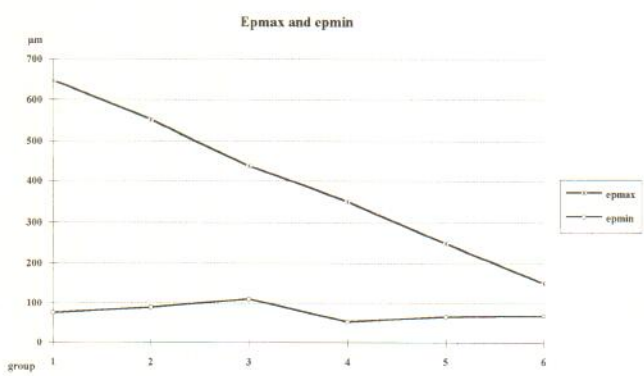

Fig. 2. Values of epmax and epmin in the different groups of patients (Table II).

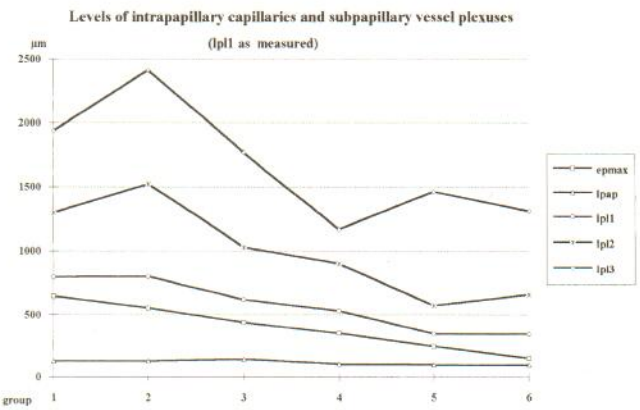

Fig. 3. Values of lpap, epmax, lpl 1, lpl 2, and lpl 3 (as measured), in the different groups (Table II).

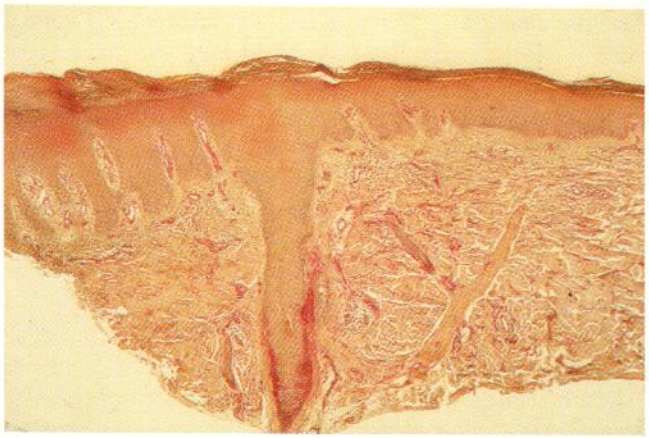

Fig. 4. Paraffin section showing the transition of a psoriatic plaque (*left*) into adjacent, clinically normal skin (*right*). lpl 1 and lpl 2 cf. Fig. 1.

ented plexus lies 800 μm below the skin surface. When epmax is less than 400 μm, at approximately this distance (900 μm from the skin surface) the second subpapillary plexus is located.

In the line-diagram in Fig. 3, the depth of the dermis is represented on the *y*-axis in 500 μm steps. Epmax, lpap, lpl 1, lpl 2 and lpl 3 are displayed as lines. From group 1 to group 6, lpap decreases slightly.

It is obvious that in groups 1, 2 and 3 there are no subpapillary vessels with a distance shorter than 500 μm to the skin surface. In groups 5 and 6, where the values of epmax drop below 300 μm, lpl 1 adopts values of less than 500 μm. Parallel lpl 2 reaches the values that lpl 1 occupied at an epmax higher than 400 μm, and lpl 3 those previously occupied by lpl 2.

Fig. 4 shows the transition of a psoriatic plaque into adjacent, clinically normal skin. Lpl 1 and lpl 2, as measured by image analysis, are displayed as lines.

Comparison of the two sides reveals that the vessels of the first subpapillary, horizontally oriented plexus on the right (healthy skin) lie inside the dermal papilla in the psoriatic lesion, with an epmax of 500 μm on the left.

Therefore this – in normal skin extrapapillary vessel is regarded as belonging to the ascending capillary of the dermal papilla in psoriatic skin. We can say that with increasing epmax

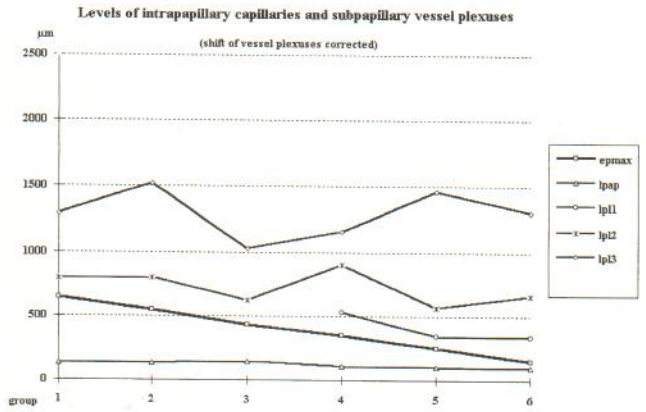

Fig. 5. Values of epmax, lpap, lpl 1, lpl 2 and lpl 3 with corrected shift of the different plexus levels. The values of lpl 1 are attributed to lpl 2 at epmax ≥ 400 μm; that of lpl 2 to lpl 3.

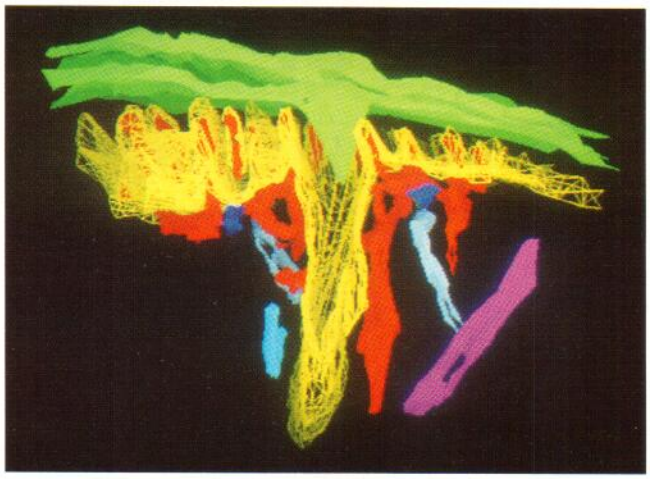

Fig. 6. 3D reconstruction of the transition of a psoriatic lesion (*left*) into adjacent, non involved skin (*right*).
green: horny layer
yellow: basement membrane
red: vessels
violet: smooth muscle.

there is an elongation of the intra-papillary capillaries due to the inclusion of the first subpapillary plexus in the dermal papillae.

As by definition, we call the distance to the uppermost recognizable subpapillary plexus pl 1, we erroneously consider in lesional skin (Fig. 4, left side) the plexus as first subpapillary plexus which corresponds to the second subpapillary vascular plexus in normal skin (Fig. 4, right side, margin of the lesion). When in psoriatic skin epmax increases above lpl 1 in non-involved skin, the designations of pl 1 and pl 2 differ from the correct plexus names by one number.

After correction of this shift we realize that lpl 1 is missing above an eprnax ≥ 400 μm (Fig. 5). The values of lpl 1 are attributed to lpl 2 at epmax ≥ 400 μm and the ones of lpl 2 to lpl 3 respectively. Fig. 5 shows that after this correction there is little variation in the levels of vascular plexuses within the dermis.

Computer-supported 3 dimensional reconstruction

The results obtained by 3-dimensional reconstruction of serial sections confirm that the upper horizontal vascular plexus dis-

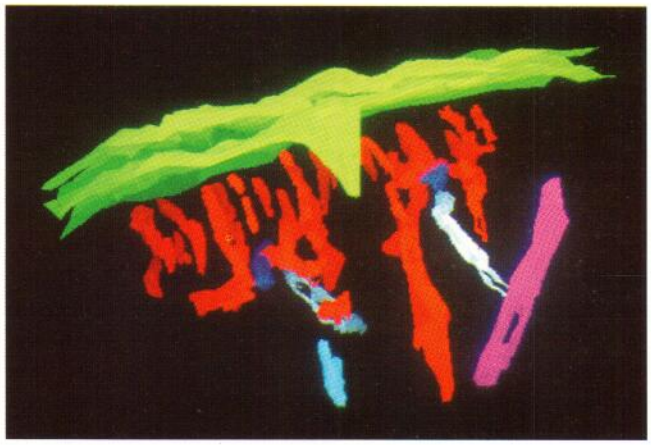

Fig. 7. The same 3D reconstruction as in Fig. 6, omitting the epidermal basement membrane.

appears due to inclusion in the dermal papillae by the acanthotic epidermis of the psoriatic plaque.

Fig. 6 shows the 3-dimensional architecture of the transition of a psoriatic lesion into adjacent, non-involved skin (the same situation is presented 2-dimensionally in Fig. 4). In the non-involved skin on the right, the horizontal cross-connections of the subpapillary plexus are located underneath the epidermis; in the psoriatic plaque on the left, they disappear in the basement membrane, displayed in yellow. The same situation, omitting the basement membrane is displayed in Fig. 7: neglecting the epidermal component there is virtually no difference in the arrangement of the vessels. Only the increasing diameters of the vascular lumina, corresponding to the dilatation of capillaries, indicate the location of the psoriatic lesion.

DISCUSSION

The subepidermal, intrapapillary capillaries in the psoriatic plaque are only seemingly elongated. This elongation is not – as previously assumed – due to a proliferation of vessels by angiogenesis (3, 5, 6), but has its reason in the inclusion of the horizontal venous plexus into the dermal papilla, normally located below the rete pegs.

The downgrowing epidermal rete pegs embrace the existing vascular structures and integrate the originally subpapillary vessels of the superficial plexus into the thus elongated papillae. In the psoriatic plaque therefore not only the intrapapillary capillaries but also the first and in extensive acanthosis even the second horizontally running vascular plexus lie within the dermal papillae. In the resolving plaque, once the epidermal thickness is reduced below 400 μm, the horizontal plexuses are again located beneath the papillae.

Braverman and Yen (5) classify the capillary loops of normal forearm skin into two segments: an intrapapillary and an extrapapillary portion. An imaginary line drawn between the deepest points of adjacent rete pegs defines these two zones. While the intrapapillary part shows the ultrastructural characteristics of an arterial capillary, after leaving the papilla, it abruptly displays venous characteristics, showing bridged fenestrations and a multilayered basement membrane.

In the psoriatic plaque, however, Braverman et al. (2, 5, 12) found that the intrapapillary capillary loops were predominantly venous capillaries, leading them to the conclusion that there is increased proliferation of the venous part of the capillaries.

Our reconstructive and histometric results indicate, however, that the intrapapillary venous capillaries described by Braverman and Yen are actually vessels of the subepidermal vascular plexus (postcapillary venules).

When the acanthosis (epmax) increases above 400 μm, the first subpapillary, horizontally oriented vascular plexus is located higher than the deepest point of the subepidermal basement membrane zone. Therefore we erroneously interpreted the vascular layer which in healthy skin is called the second vascular plexus as the first subpapillary vascular plexus in psoriatic lesions (see Figs. 3 and 4). The 3-dimensional reconstruction (see Fig. 6) confirms that the upper horizontal vascular plexus disappears in the papillary region. When we look at the microvasculature disregarding the dermo-epidermal junction (Fig. 7), there are almost no differences between involved and normal skin, i.e. a real elongation of the papillary capillaries did not take place. As the upper vascular plexus, thus integrated into the elongated papillary region, consists mainly of postcapillary venules (7, 9), the proportion of the arterial and venous limbs of the intrapapillary vessels is shifted towards the venous part.

Interestingly, in another paper Braverman states that "following three weeks of Goeckerman therapy, the morphology of psoriatic capillary loops changed from venous capillaries to arterial capillaries which are found in the papillae of normal skin" (12). Five years later together with Sibley (6) he found that this 'transformation' of venous in arterial limbs of capillaries correlates with the labelling index of the basal keratinocytes. He concluded that epidermal hyperplasia requires vascular proliferation. According to Braverman, epidermal hyperplasia causes an increase in papillary volume and height and with increasing papillary height the intrapapillary capillary loops elongate (2).

Our histometric investigations confirm the correlation between epidermal hyperplasia and papillary height. The acanthosis in the psoriatic plaque is caused exclusively by hyperplasia of the rete pegs, there is no increased thickness of the epidermal part overlaying the papillae. As epmin is relatively constant (Fig. 2), the papillary height, being the difference of epmax and epmin, is directly related to epmax. The length of the intrapapillary capillaries thus depends on epmax as well. When epmax is reduced below 400 μm, accompanied by a corresponding decrease in papillary height, the first subpapillary vascular plexus appears (Fig. 4).

The integration of the previously subpapillary vascular plexus into the papillary region also explains the low labelling index of the endothelia of psoriatic lesions after incubation with tritiated thymidine (6). As there is no proliferation of vessels in the psoriatic plaques, there is also no need for them to decompose in resolving lesions. Indeed, no necrotic endothelia could be demonstrated during healing (6): "We never observed necrosis of endothelial cells in the intrapapillary loops or a spotty return to normal within these loops".

In this connection the observations of Ryan by means of epiluminescence microscopy are interesting (13), describing the association of hyperplastic or hypertrophic papillary vessels and epidermal hypertrophy. He states that in atrophic epidermis the intrapapillary vessels appear atrophic as well, in normal skin they are normal and in epidermal hyperplasia, coiling occurs. In clinically psoriasiform appearing skin lesions, he invariably found coiled capillaries; on the other hand the psoriasiform aspect could never be seen when coiled capillaries were lacking (14). Whether there is altered density of capillaries in psoriatic plaques is not yet clear.

While some authors favour an increased capillary density (4), others speak of convolute formation. Based on observations by epiluminescence, Schlosser and Pullmann (4) reported in initial poriasis compared with normal skin an actual increase in capillary density caused by angiogenesis. Comparing initial with fully developed psoriatic lesions, however, the authors felt that the further increase in capillaries was due to convolute formation of the capillaries, though they could not definitely exclude angiogenesis.

Barton et al. (1) compared capillaries microscopically in 20

psoriasis patients and 10 healthy control subjects. They found a successive increase in the number of capillary profiles from normal skin to non-involved skin at the margin between psoriatic plaques and lesional psoriatic skin. The authors concluded that there is increased vascular material as well as dilatation of vessels in psoriatic skin. It is not clear, however, whether they evaluated the complete biopsies or a defined area of the dermis.

Our findings inevitably lead to the question which has been discussed for decades: whether psoriasis starts from the epidermis or from the vasculature. What hyperplasia is concerned we can answer this question: the vessels do not proliferate, at least not the same extent as the epidermis. What the role of the endothelial cells is concerned with, regarding their activation and their immunologic part in psoriasis (15, 16), no conclusion can be drawn from our histological and histometric results or from the 3-dimensional reconstructions.

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