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Hidradenitis suppurativa/acne inversa: bilocated epithelial hyperplasia with very different sequelae

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Summary

Background Hidradenitis suppurativa/acne inversa is a chronic, inflammatory, scarring disease in the terminal hair follicle and apocrine gland-bearing areas (skin folds). There is considerable histological evidence that perifolliculitis and follicular hyperkeratosis precede the rupture of the follicle. The timing of the epithelial hyperplasia at the infundibula of inflamed terminal follicles has not yet been clarified.

Objectives To clarify the early histopathological life of lesions ('chronology') in hidradenitis suppurativa/acne inversa, focusing on the terminal follicle structure and its surrounding tissue (hyperkeratosis, hyperplasia of follicular epithelium, perifolliculitis and rupture).

Methods In total, 485 operative specimens obtained from 128 patients with diagnosed hidradenitis suppurativa/acne inversa (all surgically treated by wide excision) were examined histologically. Two to five histological preparations (total 485) per operation area (total 196) were prepared by multiple slicing.

Results Hidradenitis suppurativa/acne inversa showed a heterogeneous histological pattern: hyperkeratosis of the terminal follicles (89%), hyperplasia of follicular epithelium (80%), pronounced perifolliculitis (68%) and follicle rupture (24%). Perifolliculitis, follicular hyperkeratosis and hyperplasia occurred prior to the rupture of the follicle. Other histological criteria were: subepidermal cellular inflammatory infiltrate (82%), epidermal psoriasiform hyperplasia (56%), pronounced acute dermal inflammation (28%), pronounced chronic dermal inflammation (49%), and involvement of apocrine glands (52%) and subcutis (31%).

Conclusions Infundibular hyperkeratosis, hyperplasia of the follicular epithelium and perifolliculitis are major histopathological characteristics of hidradenitis suppurativa/acne inversa. These apparently precede rupture of the follicle. In particular, hyperplasia of the follicular epithelium probably marks the beginning of sinus formation, which usually spreads horizontally. Psoriasiform hyperplasia of the interfollicular epidermis with subepidermal inflammatory infiltrate might be interpreted as an inflammation-driven process basically identical to that which is evident at the terminal follicle. However, it does not lead to harmful and progressive sequelae like those (rupture, sinus tracts) seen at the terminal follicles.

Hidradenitis suppurativa/acne inversa is a chronic, inflammatory, scarring disease with topographical predilection for skin folds (axillary, submammary, inguinal, anogenital).[1–4] These different anatomical regions affected by the disease show histopathological homology.[5] In our recent examination of operative material from 60 patients we identified two primary histotopographical foci:[6] (i) infundibulum of terminal hair follicle with hyperkeratosis ('follicular plugging') and epithelial hyperplasia; and (ii) interfollicular epidermis with psoriasiform hyperplasia. Both 'regions of interest' were accompanied by an inflammatory mixed infiltrate with selective CD8 cell epitheliotropism.[6] Our results concerning the terminal hair follicle indicated that perifolliculitis and hyperkeratosis precede its rupture.

The timing of epithelial hyperplasia at the infundibula of inflamed terminal follicles has not yet been clarified. Thus, the question arises as to whether this hyperplasia is a precursor of follicular rupture and resultant dermal spreading of the inflammation, which would indicate a potential therapeutic target in the early stages of the disease. To clarify this,

we examined a much greater number of operative samples (from 128 patients) than in our earlier study (60 patients).

Material and methods

We examined histologically a total of 485 operative specimens obtained from 128 patients (62 women, 66 men) with the diagnosis of hidradenitis suppurativa/acne inversa (all surgically treated by wide excision in our clinic from January 1996 to November 2009). The mean age in both sexes at the time of operation was 34·5 years (median 34). The mean duration of illness from the first clinical signs to the surgical intervention described was 7·4 years (median 7) in both sexes. At the time of surgery, 91% (116/128) of the patients were smokers [women: 84% (52/62); men: 97% (64/66)]. Eighty-four per cent (107/128) of the patients presented with the disease at the time of surgery on at least two typical body areas (among them there was also bilateral axillary manifestation).

In total, 485 operative specimens from 196 different areas (i.e. 196 different operative fields: 86 axillary, 67 inguinal, 43 anogenital) of 128 patients were examined three times (two investigators each performed three independent examinations at three different time points). Microscopy was performed at 6·3×, 12·5× and 25× magnification. All specimens had been fixed in 4% formaldehyde and embedded in paraffin. Sections were stained with haematoxylin and eosin. Two to five histological preparations (total 485) per operation area (total 196) were prepared by multiple slicing. The focus of the study was on the terminal follicle structure and its surrounding tissue (hyperkeratosis, hyperplasia of follicular epithelium, perifolliculitis and rupture). Other histological criteria already described in the literature[3,5–11] were also investigated (Table 1). Results concerning hyperkeratosis, hyperplasia, perifolliculitis, epidermal hyperplasia and subepidermal inflammation have been partially described previously in 60 of the 128 patients.[6]

Results

The main qualitative and quantitative data are depicted in Tables 1–3 and in Figures 1–3. Hyperkeratosis of the terminal follicles in lesser or greater intensity was found in 89% (175/196) of the specimens. Hyperplasia of follicular epithelium of various degrees (mild/pronounced) was evident in 80% (157/196). Pronounced perifolliculitis [accumulation of inflammatory cells (> 150) in the perifollicular region] was observed in 68% (133/196) of the specimens. Follicle ruptures were found in 24% (47/196) of the tissue samples. Seventy-three per cent (128/175) of the specimens with follicular hyperkeratosis (mild and pronounced) showed pronounced perifolliculitis, and no signs of follicular rupture

Table 1 Hidradenitis suppurativa/acne inversa: histological findings in operative specimens (n = 196)

Histological criteria	Severity	n (%)
Follicular hyperkeratosis	None	21/196 (11)
	Mild	77/196 (39)
	Pronounced	98/196 (50)
Hyperplasia of follicular epithelium	None	39/196 (20)
	Mild/pronounced	157/196 (80)
Perifolliculitis	None/mild (≤ 150 inflammatory cells)	63/196 (32)
	Pronounced (> 150 inflammatory cells)	133/196 (68)
Rupture	No	149/196 (76)
	Yes	47/196 (24)
Subepidermal cellular inflammatory infiltrate	No	36/196 (18)
	Yes	160/196 (82)
Psoriasiform epidermal hyperplasia	No	87/196 (44)
	Yes	109/196 (56)
Subepidermal cellular inflammatory infiltrate plus epidermal psoriasiform hyperplasia	No	93/196 (47)
	Yes	103/196 (53)
Acute inflammation of the dermis	None or only focal	46/196 (24)
	≤ 50% of the dermis involved	95/196 (48)
	> 50% of the dermis involved	55/196 (28)
Chronic inflammation of the dermis	None	25/196 (13)
	≤ 50% of the dermis involved	74/196 (38)
	> 50% of the dermis involved	97/196 (49)
Involvement of the apocrine glands (surrounding inflammation, stasis, hyperplasia, dilatation)	No	94/196 (48)
	Yes	102/196 (52)
Inflammation of the subcutis	No	135/196 (69)
	Yes	61/196 (31)

Table 2 Hidradenitis suppurativa/acne inversa: histopathological criteria at the terminal hair follicle structure

Criteria	n (%)
Infundibular hyperkeratosis	
Yes	175/196 (89)
No	21/196 (11)
Infundibular hyperkeratosis + perifolliculitis	
Yes	128/175 (73)
No	47/175 (27)
Infundibular hyperkeratosis + perifolliculitis + no signs of follicular rupture	
Yes	88/128 (69)
No	40/128 (31)
Infundibular hyperkeratosis + perifolliculitis + no signs of follicular rupture + follicular hyperplasia	
Yes	62/88 (71)
No	26/88 (29)

Table 3 Hidradenitis suppurativa/acne inversa: histopathological criteria and their relationship to the duration of illness

		Duration of illness (years)	
Histological criteria	Severity	Mean	Median
Follicular hyperkeratosis	None	3·6	2·5
	Mild	6·2	4
	Pronounced	12·6	8
Inflammation of the subcutis	No	7·8	3·75
	Yes	8·9	5·5
Involvement of the apocrine glands	No	10·4	5
	Yes	7·9	4·5

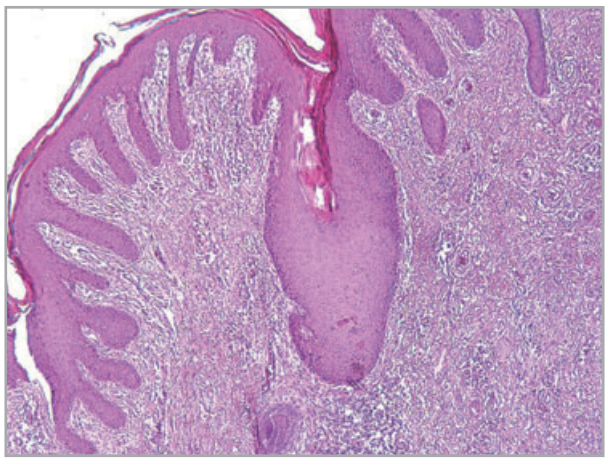

Fig 1. Bilocated hyperplasia (epidermis and follicle) and perifolliculitis at the infundibulum of the terminal follicle (haematoxylin and eosin; original magnification × 6.3; case number 2001/3384a).

were evident in 69% (88/128) of these. However, follicular hyperplasia was striking in 71% (62/88) of this subgroup (Table 2).

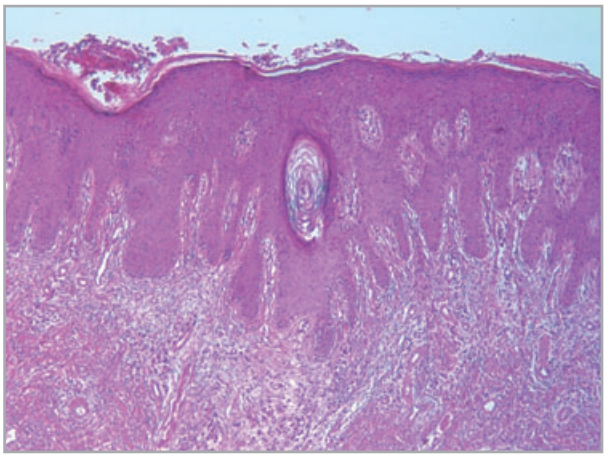

Fig 2. 'Psoriasiform' (equally long rete ridges) epidermal hyperplasia (haematoxylin and eosin; original magnification × 6.3; case number 2009/805a).

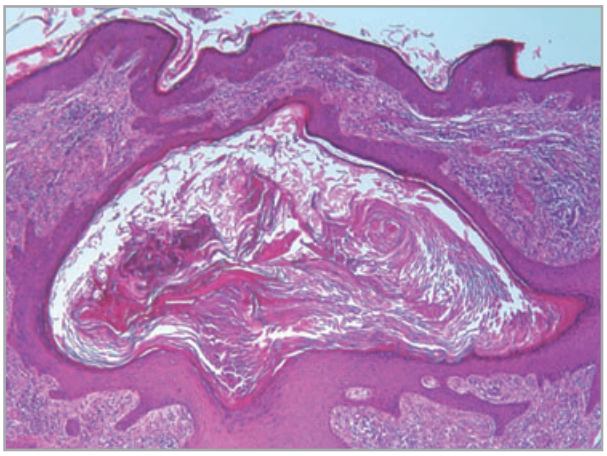

Fig 3. Hyperplasia and hyperkeratosis of a terminal hair follicle (draining to the surface) and the start of sinus formation (haematoxylin and eosin; original magnification × 6.3; case number 2009/2273a).

A subepidermal cellular inflammatory infiltrate in the area of the interfollicular epidermis was observed in 82% (160/196) of the tissue samples, and a psoriasiform epidermal hyperplasia with equally extended rete ridges in 56% (109/196) of the preparations (parahyperkeratosis was lacking and the stratum granulosum was intact). A combination of these two conditions was found in 53% (103/196) of the entire operative material. An acute inflammation of the dermis, covering more than 50% of the total dermal area, was seen in 28% (55/196), and a chronic fibrosing inflammation affecting more than 50% of the dermal area was visible in 49% (97/196) of the specimens. Apocrine glands were involved (surrounding inflammation, stasis, hyperplasia) in 52% (102/196) and the subcutis (inflammation) in 31% (61/196) of the specimens.

The severity of the follicular hyperkeratosis increased with the duration of the disease**,** whereas inflammation of the

subcutis or involvement of the apocrine glands showed only marginally longer or no longer duration of the disease (Table 3).

Discussion

The examination of the operative material from more than double the previous number of cases[6] confirmed the high prevalence of the following histopathological details: infundibular hyperkeratosis (89%), hyperplasia of the follicular epithelium (80%), perifolliculitis (68%), and interfollicular psoriasiform epidermal hyperplasia with subepidermal inflammatory infiltrate (53%). As a comparison, Jemec and Hansen[9] described infundibular hyperkeratosis ('poral occlusion', 17/60) and folliculitis (without poral occlusion, 17/60) as the most frequently occurring features in hidradenitis suppurativa/acne inversa in their study of 60 biopsies. Boer and Weltevreden[10] showed a correlation between perifolliculitis, spongiform infundibulofolliculitis and hyperkeratosis (occlusion) in 95% of the 39 biopsies in their study. The most frequent phenomenon, follicular hyperkeratosis, which we also confirmed and which seems to become more severe the longer patients have the disease, could be the result of increased endogenous acetylcholine production due to exogenous nicotine mediated by the local influence of *Staphylococcus aureus*.[12,13] Our study also confirmed the early perifollicular inflammation with a lymphocytic character which had already been recognized, as well as the involvement of the subcutis and the apocrine glands (both seem to be independent of the duration of illness).[3,6,9,10,14,15] In our observation, 52% of the apocrine glands were morphologically involved in the disease. The thesis that apocrine glands are the focus of the pathogenetic process resulted in the term hidradenitis suppurativa. The name acne inversa was coined when Yu and Cook[7] described the terminal follicle as the main histopathological target.[3] In any case, both terms are found in the literature and there is still discussion about the correct nomenclature.[4,15] As to that, our results might confirm the term acne inversa (and underline the secondary involvement of the apocrine glands), but it is still unclear why disease takes place in areas rich in apocrine glands where they form an anatomical unit with the terminal follicles. The potential role of the glands in connection with nicotine secretion has been discussed previously.[6,12,13] Future investigations should deal with the composition of the secretion of the apocrine glands as well as their ultrastructure in unaffected skin areas in patients with hidradenitis suppurativa/acne inversa.

The follicular epithelial hyperplasia, which was secondarily documented in figures in earlier articles,[6,16] was found with high prevalence in the more extensive material in this study and was found to be an essential structural element at the follicular target. In the time sequence, it apparently precedes rupture of the follicle and probably represents the start of the sinus formations (sinus tracts), which usually spread horizontally. Thus, rupture indicates a secondary development (a 'point of no return') of suppurative and ultimately scarring inflammation with prolonged confinement to the dermis (long-term abscessing disease spreading horizontally within the dermis). Psoriasiform hyperplasia of the interfollicular epidermis with subepidermal inflammatory infiltrate is also confirmed.[6] This might be interpreted as an inflammation-driven process basically identical to that which is evident at the terminal follicle. It is, however, merely psoriasis-like and not real psoriasis vulgaris. Clinically, the prevalence of manifest psoriasis vulgaris was 3·9% (5/128) in these patients. The disease was expressed in typical locations, but the affected flexural areas of hidradenitis suppurativa/acne inversa did not show a typical erythematosquamous psoriatic appearance. Additionally, in histology the stratum granulosum is still present and there is no hyperkeratosis and no parakeratosis.

However, epidermal hyperplasia does not lead to harmful and progressive sequelae, such as those (rupture, sinus tracts) seen at the infundibular terminal follicles with resulting sinus tracts and ultimate perforation. Interestingly, both regions (follicle and interfollicular epidermis) have niches of stem cells[17] which might enable an inflammation-induced hyperplasia of keratinocytes. Gniadecki and Jemec[18] reported a possible involvement of 'stem cell-like keratinocytes' in the overall histopathological process with the development of sinus tract formations. If this theory is correct, the early bilocated identical lymphocytic inflammation[6] with a supposed specific cytokine milieu should be a therapeutic target for disease intervention, well in advance of the wide surgical excision of late stages.

What's already known about this topic?

- Hidradenitis suppurativa is a chronic, inflammatory disease in the terminal hair follicle-bearing areas.
- The timing of the epithelial hyperplasia at the infundibula of inflamed follicles has not been clarified.

What does this study add?

- Epithelial hyperplasia apparently precedes rupture of the follicle and probably represents the start of the sinus formation.
- Interestingly, this region has niches of stem cells which might enable an inflammation-induced hyperplasia of keratinocytes. This could be a therapeutic target.

Acknowledgments

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References

1 Jansen T, Plewig G. Acne inversa. *Int J Dermatol* 1998; **37**:96–100.
2 Jansen T, Plewig G. What's new in acne inversa (alias hidradenitis suppurativa)? *J Eur Acad Dermatol Venereol* 2000; **14**:342–3.

3 Plewig G, Steger M. Acne inversa (alias acne triad, acne tetrad or hidradenitis suppurativa). In: *Acne and Related Disorders* (Marks R, Plewig G, eds). London: Martin Dunitz, 1989; 345–57.
4 Revuz J. Hidradenitis suppurativa. *J Eur Acad Dermatol Venereol* 2009; **23**:985–98.
5 Jemec GB, Thomsen BM, Hansen U. The homogeneity of hidradenitis suppurativa lesions. A histological study of intra-individual variation. *APMIS* 1997; **105**:378–83.
6 Laffert MV, Helmbold P, Wohlrab J *et al.* Hidradenitis suppurativa (acne inversa): early inflammatory events at terminal follicles and at interfollicular epidermis. *Exp Dermatol* 2010; **19**:533–7.
7 Yu CC, Cook MG. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* 1990; **122**:763–9.
8 Sellheyer K, Krahl D. Hidradenitis suppurativa is acne inversa! An appeal to (finally) abandon a misnomer. *Int J Dermatol* 2005; **44**:535–40.
9 Jemec G, Hansen U. Histology of hidradenitis suppurativa. *J Am Acad Dermatol* 1996; **34**:994–9.
10 Boer J, Weltevreden EF. Hidradenitis suppurativa or acne inversa. A clinicopathological study of early lesions. *Br J Dermatol* 1996; **135**:721–5.
11 Attanoos RL, Appleton MAC, Douglas-Jones AG. The pathogenesis of hidradenitis suppurativa: a closer look at apocrine and apoeccrine glands. *Br J Dermatol* 1995; **133**:254–8.
12 Kurzen H, Wessler I, Kirkpatrick CJ *et al.* The non-neuronal cholinergic system of human skin. *Horm Metab Res* 2007; **39**:125–35.
13 Hana A, Booken D, Henrich C *et al.* Functional significance of non-neuronal acetylcholine in skin epithelia. *Life Sci* 2007; **80**:2214–20.
14 Plewig G. Acne inversa, Acne keloidalis nuchae, abszedierende Follikulitis der Kopfhaut: Ein verbindendes Konzept. In: *Fortschritte der praktischen Dermatologie und Venerologie* (Plewig G, Prinz J, eds), Vol. 18. Berlin: Springer, 2003; 192–203.
15 Kurzen H, Kurokawa I, Jemec GBE *et al.* What causes hidradenitis suppurativa? *Exp Dermatol* 2008; **17**:455–72.
16 Layton A. Pathology of hidradenitis suppurativa. In: *Hidradenitis Suppurativa* (Jemec GBE, Revuz J, Leyden JJ, eds). New York: Springer, 2006; 25–33.
17 O'Shaughnessy RFL, Christiano AM. Stem cells in the epidermis. *Skin Pharmacol Appl Skin Physiol* 2001; **14**:350–7.
18 Gniadecki R, Jemec GBE. Lipid raft-enriched stem cell-like keratinocytes in the epidermis, hair follicles and sinus tracts in hidradenitis suppurativa. *Exp Dermatol* 2004; **13**:361–3.