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The pathogenesis of hidradenitis suppurativa: a closer look at apocrine and apoeccrine glands

R.L.ATTANOOS, M.A.C.APPLETON AND A.G.DOUGLAS-JONES

Department of Histopathology, University Hospital of Wales, Heath Park, Cardiff CF4 4XN, U.K.

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Summary We undertook a retrospective pathological study of 118 skin resection specimens from 101 patients with hidradenitis suppurativa. Follicular occlusion was identified in all the specimens, regardless of disease duration (1 month to 18 years), but was not noted in the axillary and inguinal skin of controls. We therefore regard follicular occlusion as an early and important feature in the pathogenesis of the disease. The presence of apoeccrine glands in axillary skin provided an *in vivo* model to directly observe the effects of follicular occlusion on follicle inflammation and apocrine gland destruction. In the majority of cases, active folliculitis was associated with apocrinitis and apocrine destruction, whereas apoeccrine glands, which drain directly on to the epidermal surface, appeared intact and non-inflamed. These observations provide direct evidence in an *in vivo* model that follicular occlusion by keratinous material, with subsequent active folliculitis and secondary destruction of the skin adnexae and subcutis, occur as an integral step in the pathogenesis of hidradenitis suppurativa.

Hidradenitis suppurativa is a chronic, inflammatory, scarring disease of apocrine sweat gland-bearing skin. The diagnosis of the disease is primarily clinical,[1] based on the presence of multiple abscesses and sinuses, which often show a poor response to conventional antibiotics and a tendency to recur. The onset is predominantly after puberty, although it has been described in neonates. In women, premenstrual exacerbation of the disease is not uncommon.

A number of histopathological changes have been identified in resection specimens,[2] but these are considered to be non-specific, and represent the late sequelae of the disease in many cases.

The pathogenesis of the condition remains unclear. The anatomical distribution of the disease suggests that it is primarily a disorder of apocrine glands, and the term 'apocrinitis' has been employed as a synonym for the condition. Indeed, the presence of distended apocrine glands containing polymorph neutrophils was demonstrated in an early description of the disease by Brunsting in 1939.[3] More recent publications[4,5] have suggested that follicular occlusion in apocrine gland-bearing skin is the likely primary event, followed by secondary suppuration and sinus formation. However, these notions are based on the end-stage histological appearances in hidradenitis suppurativa, and direct pathological evidence of disease evolution is lacking. The association with, and clinical similarity of hidradenitis suppurativa to, acne conglobata, dissecting cellulitis of the scalp, and pilonidal sinus (follicular occlusion-related diseases), lends circumstantial support to this view of the aetiology of the condition. Disturbances in androgen metabolism have highlighted an endocrine component in the condition,[6,7] but their part in its pathogenesis remains uncertain.

The aim of the present study was to review the skin resection specimens from 101 patients with hidradenitis suppurativa of variable duration, describe the morphological variation of the pathology at each site, and gain insight into the pathogenesis of the disease. To this end, particular attention was paid to the adnexae and, in the axillae, the apoeccrine sweat glands.[8] The presence of apoeccrine sweat glands in axillary skin provides, for the first time, an *in vivo* model to study the direct effect of follicular occlusion on apocrine glands. The ducts of apocrine glands drain into the main follicle, and secretion reaches the skin surface by way of the hair shaft. Hence, follicular occlusion will cause obstruction of apocrine and sebaceous secretion. In contrast, apoeccrine glands structurally combine features of both apocrine and eccrine glands, with an apocrine secretory coil exhibiting 'decapitation' secretion, and a straight intradermal duct which opens directly on to the epidermal surface, circumventing the effect of

terminal follicular occlusion. Comparison of inflammation and destruction in apocrine and apoeccrine glands in hidradenitis suppurativa cases with control cadaveric skin provided the basis for the study of the pathogenesis of this condition.

Methods

One hundred and eighteen resection specimens from axillary, inguinoperineal, perianal, mammary and vulval skin were reviewed simultaneously by two pathologists (R.L.A. and M.A.C.A.). Specimens were fixed in 10% formalin, and routinely processed. Five-micron sections were stained with haematoxylin and eosin for morphological assessment. Details regarding the nature, distribution and extent of the inflammatory cell infiltrate were noted. Granulomatous reactions were classified into foreign-body or epithelioid types. Particular attention was paid to morphological abnormalities of the adnexae. By careful serial sectioning, apocrine glands, eccrine glands, and the recently described apoeccrine glands were delineated.

The presence/absence of epidermal changes, particularly follicular occlusion, hyperplasia and keratinocyte atypia was documented, and features such as epidermal cyst formation, sinus tracks, fibrosis and fat necrosis were also noted. The histological changes were compared with control specimens of axillary and inguinoperineal skin taken from 10 cadavers with no documented history of hidradenitis suppurativa.

Results

Clinical results

The study group comprised 79 women and 22 men. Fifty-three patients (52·5%) had axillary disease, which was bilateral in 29 cases. Hidradenitis affecting the inguinoperineal and perianal skin was noted in 47 and seven patients, respectively. Six female patients had infra-mammary disease, and five had vulval skin involvement. Multiple site disease was noted in 12 cases. The duration of disease varied from 6 months to 18 years.

The control group comprised four women and six men.

Table 1. Histopathological appearances in hidradenitis suppurativa

	Axilla	Perineal	Perianal	Mammary	Vulval
Cases	53	47	7	6	5
Dermis					
Normal	7	3	0	1	0
Fibrosis	46	44	7	6	5
Epidermal cyst	25	15	1	1	1
Sinus track	20	20	6	3	3
Acute inflammation	13	9	0	1	1
Chronic inflammation	15	14	2	1	1
Abscess	37	32	5	4	4
Foreign-body granuloma	14	12	0	2	1
Epithelioid granuloma	4	3	1	0	2
Fibrinoid vasculitis	0	0	0	0	0
Adnexae					
Normal pilar units	9	12	2	2	1
Perifolliculitis	34	31	5	4	4
Normal apocrine units	36 (70%)	19 (40%)	3 (43%)	1 (17%)	2 (40%)
Apocrine inflammation	14	0	0	0	0
Normal eccrine units	31	30	6	1	3
Eccrine inflammation	17	9	1	3	0
Apoeccrine glands	15 (30%)	0	0	0	0
Apoeccrine inflammation	0	0	0	0	0
Subcutis					
Normal	30	21	2	5	4
Fibrosis	17	20	5	0	1
Fat necrosis	13	13	1	1	1
Inflammation	2	2	0	0	0

Pathological results

A detailed histopathological evaluation of the 118 resection specimens is shown in Table 1.

In all of the study cases a significant degree of follicular plugging was identified; when prominent, this was manifested as large cystic lesions, many of which contained refractile laminated keratin and hair shafts. Skin from all sites exhibited varying degrees of inflammation and reparative fibrosis of both the dermis and subcutis. The presence of 'established' epidermal cysts was found to be less common. Acutely inflamed sinus tracks were also noted as a frequent feature, occurring predominantly in the extra-axillary sites and in those subjects with long-standing disease. Adnexal inflammation, a common feature, was most frequently perifollicular in distribution, occurring in 64% of axillary cases and 66% of inguinoperineal cases. In perianal, mammary and vulval skin, an active folliculitis was noted in 71, 67 and 83% of cases, respectively.

Active inflammation of the sweat glands was less common in all sites, and where present was more frequently eccrine than apocrine in distribution. At no site was the inflammation solely seen around apocrine glands. Indeed, the axilla was the only site in which active destruction of apocrine glands by polymorph neutrophils was noted, occurring in 26% of cases. Peri-eccrine inflammation was identified in 32% of axillary specimens. When present, active apocrinitis was invariably associated with severe acute inflammation in the adjacent hair follicle (Fig. 1). In 15 of 53 (30%) axillary specimens, unaffected secretory tubules displaying 'decapitation' secretion (apocrine gland-type) were seen to drain directly on to the epidermal surface via a straight intradermal duct lined by eccrine duct epithelium. Morphologically, these sweat glands corresponded to so-called apoeccrine glands (Fig. 2). Apoeccrine glands were not identified in extra-axillary sites.

No chronological pattern to these changes could be identified in any site, and there was no significant difference between the sexes.

Foreign-body type granulomas containing refractile keratinous material around ruptured hair follicles and sinus tracks were identified in approximately 25% of all specimens. No granulomatous inflammation near sweat glands was identified. The presence of discrete epithelioid granulomas in the deep dermis and subcutis, away from the site of active inflammation, was infrequently seen (8% of all specimens). One female patient with

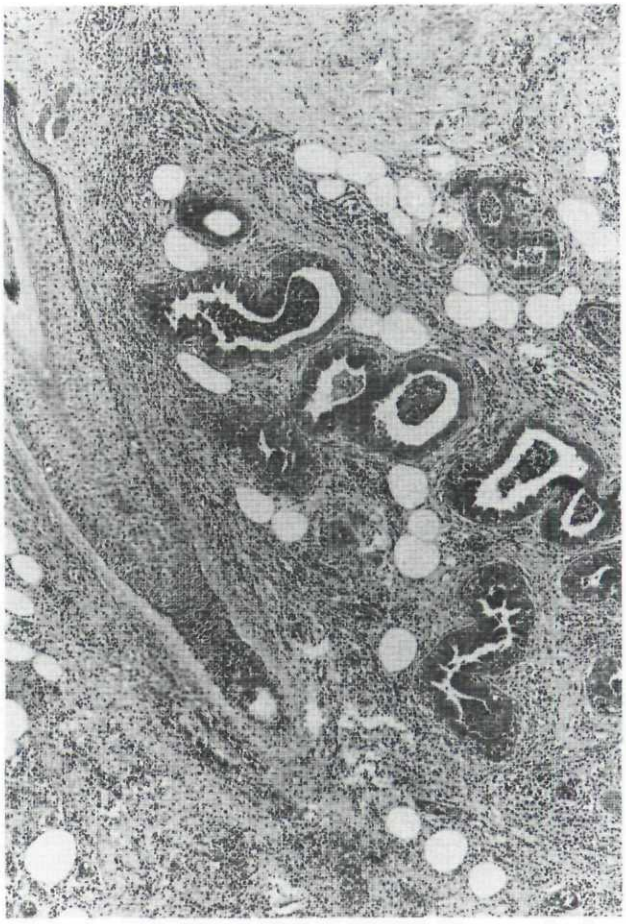

Figure 1. Abscess formation and active folliculitis, with adjacent infiltration of apocrine glands by polymorph neutrophils (haematoxylin and eosin ×250).

discrete epithelioid granulomas had axillary hidradenitis suppurativa and concomitant pulmonary sarcoidosis, and another with inguinoperineal hidradenitis suppurativa had colonic Crohn's disease. No systemic disease was identified in the remaining patients whose resection specimens showed epithelioid granulomas. A careful search for tubercle bacilli and fungal organisms was undertaken in all granulomatous reactions devoid of foreign-body material.

The degree of epidermal change varied. Despite the universal presence of follicular plugging in all affected sites, hyper- and parakeratosis were infrequently identified. However, acanthosis was more common, especially in vulval and perianal skin. Similarly, pseudoepitheliomatous hyperplasia was relatively more prominent in these sites, and in the inguinoperineal region. In one perianal and one vulval case of chronic hidradenitis suppurativa, invasive squamous cell carcinoma had developed. In both patients the

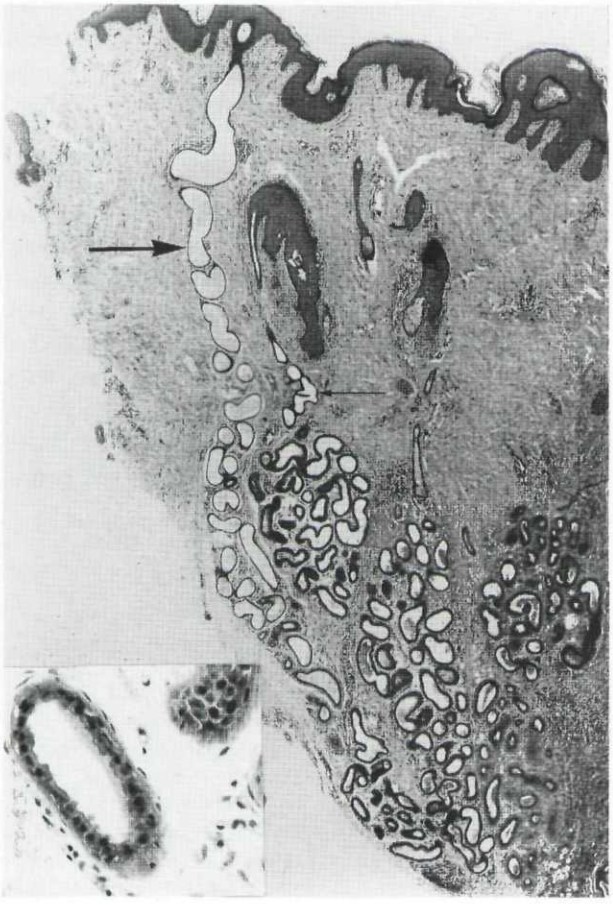

Figure 2. Apoeccrine (bold arrow) and adjacent apocrine glands (thin arrow) in skin from near the margin of a resection specimen. No active inflammation is seen in this field (×40). Inset shows high-power view of apoeccrine secretory tubule exhibiting focal decapitation secretion (haematoxylin and eosin ×400).

hidradenitis had involved multiple sites, and was of long duration (mean 15 years). In both cases, surgical resection of the well-differentiated squamous cell carcinomas resulted in a favourable outcome.

In the control specimens, no follicular plugging, epidermal cysts, sinus tracks or adnexal changes were identified. Intact and non-inflamed apocrine, eccrine and pilosebaceous units were noted in all 10 cases. Apoeccrine glands were seen in eight of the 10 cases when multiple sections were surveyed. Moderate epidermal hyperkeratosis was noted in both the axillary and perineal skin from an obese male cadaver. No follicular plugging was seen in this case.

Discussion

The histopathological findings in hidradenitis suppurativa appear to be diverse and non-specific. The only consistent feature at all sites was marked follicular plugging. The universal finding of such a feature, particularly in view of its absence in the control series, suggests that it is both an early and essential element in the pathogenesis of hidradenitis suppurativa. A deep folliculitis was identified in approximately two-thirds of the resection specimens, and there was no significant sex or site variation in this finding. In agreement with Yu and Cook,[5] we consider that hidradenitis suppurativa should be regarded as a primary folliculitis, and that apocrine inflammation and destruction follows as a secondary phenomenon.

Indeed, acute inflammation of apocrine glands was an uncommon finding, and did not appear to occur in the absence of an adjacent folliculitis in the draining pilosebaceous unit. The presence of apoeccrine sweat glands in axillary skin appears to have provided a useful *in vivo* model to study the direct effect of follicular occlusion on apocrine glands. Apoeccrine glands are thought to develop from eccrine glands at puberty, and constitute up to 45% of the axillary apocrine sweat glands, but they have not been identified in extra-axillary sites.[8] By multiple sectioning of the axillary skin, we demonstrated intact and non-inflamed apocrine secretory tubules exhibiting 'decapitation' secretion in 70% of our subjects (Table 1), and in all of the control cases. Normal/unaffected apoeccrine glands could be identified in the axillary skin in 15 of 53 (30%) and eight of 10 (80%) of the hidradenitis and control cases, respectively. In the extra-axillary sites, uninvolved apocrine glands were found in 40% of perineal hidradenitis, 43% of perianal hidradenitis, 17% of mammary hidradenitis, and 40% of vulval hidradenitis cases. The mean percentage of normal apocrine glands in the extra-axillary sites was 35%. In the axillae, apocrine glands are affected by follicular occlusion and folliculitis at an early stage, due to the direct continuity of the apocrine duct and follicular infundibulum. In contrast, apoeccrine glands remain intact until end-stage disease, because the straight intradermal duct opens directly on to the epidermal surface, providing a patent 'outlet' for the irritant apocrine sweat. Apoeccrine glands could, of course, be involved by inflammation secondarily as 'innocent bystanders'. According to this model, there would be a high proportion of apoeccrine glands among the surviving unaffected glands in axillary hidradenitis suppurativa. It was not possible to accurately type all of the surviving glands in hidradenitis suppurativa patients, because this would have required visualization of the duct of every gland. However, surviving apoeccrine

glands were seen in a significant proportion of hidradenitis specimens (30%), and this observation lends support to the above model.

The stimulus for initial follicular occlusion remains undetermined. Obesity is common in hidradenitis suppurativa, and is likely to contribute to its pathogenesis. Obesity increases skin contact, and promotes both epidermal desquamation and hyperkeratosis. Keratin hydration would be enhanced in the sweat gland-rich regions of the body, and this has been shown to reduce the width of the pilosebaceous duct orifice, favouring poral occlusion.[9] Epidermal hyperkeratosis was noted in one obese control subject, but there was no evidence of poral occlusion. This suggests that the mechanical epidermal and follicular changes described above are insufficient alone to explain the poral occlusion. Obesity is also known to alter the metabolism and activity of sex hormones, producing a state of relative androgen excess, and inducing hirsutism in women. This may produce marked coarsening of the hair shaft and subsequent follicular plugging. Hidradenitis has been successfully controlled in some female patients by anti-androgen therapy.[10]

In the present series, foreign-body-type granulomas were found in 25% of the specimens in close relation to ruptured hair follicles and epidermal cysts. Foamy macrophage-type granulomas have been described[11] in relation to apocrine sweat glands in the dermis, but were not seen in our specimens. However, the experimental model used by Shelley and Cahn[11] incorporated manual depilation of the skin and the use of atropine-impregnated tape, both of which may have stimulated an abnormal pathophysiological process. It is of interest that discrete epithelioid granulomas in two patients with systemic granulomatous disease were noted (one case of sarcoidosis and the other of Crohn's disease). These findings have been published in our earlier work.[12]

Squamous cell carcinoma arising in hidradenitis suppurativa is a recognized complication, which was seen in two of 118 specimens (1·7%). Jackman[13] observed four cases of squamous cell carcinoma in a series of 125 perianal hidradenitis specimens, and all of these cases had long-standing disease (19–32 years) prior to the development of malignancy.

It is of interest that both our cases of squamous cell carcinoma developed in non-axillary sites, suggesting that malignant change in hidradenitis suppurativa is more common in the perianal area. Squamous cell carcinoma is an uncommon but recognized complication in areas of chronic injury or irritation, and occurs in stasis ulcers, burn scars, and chronically inflamed fistulae.[14]

We have demonstrated that occlusion of hair follicles is an early and important aspect of the pathogenesis of hidradenitis suppurativa. An active deep folliculitis was observed in all cases where apocrine gland inflammation was present, indicating that apocrine destruction represented a secondary process. In a significant number of axillary cases (30%), intact apoeccrine glands were seen, which lends support to our *in vivo* model for studying the direct effect of follicular occlusion on apocrine glands and their part in the pathogenesis of hidradenitis suppurativa.

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