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Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands

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SUMMARY

A retrospective study was made of the histopathology of axillary skin excised fom 12 patients with hidradenitis suppurativa. In the majority of cases (10 out of 12), squamous epithelium-lined structures, in the form of cysts or sinuses were identified in the dermis. Laminated keratin was present in all these structures and half of the cysts also contained hair shafts, suggesting that they are derived from hair follicles. Only a small proportion of cases (4 out of 12) displayed inflammation in apocrine glands, and in these the inflammation was also seen around eccrine glands, hair follicles and the epithelium-lined structures. However, in cases where the epithelium of the 'cysts' was disrupted, the inflammatory infiltrate appeared to be centred around these areas. These observations suggest that the squamous epithelium-lined structures, which probably represent abnormal dilated hair follicles, are a more constant diagnostic feature in hidradenitis suppurativa than inflammation of apocrine glands which appears to be a secondary phenomenon.

Hidradenitis suppurativa was first described as a distinct entity by Velpeau[1] in 1839. He reported a patient with an inflammatory process involving the skin of the axillary, mammary and perianal areas. Verneuil,[2] in 1854, described a series of patients with similar lesions and was the first to suggest that they were abscesses of the sweat glands. However, it was not until 1922 that hidradenitis became associated with the apocrine glands.[3] A detailed description of the histology in hidradenitis suppurativa was made by Brunsting.[4] He observed that the earliest cellular reaction was in the subcutis, primarily within the lumen of the apocrine glands and in the neighbouring peri-glandular connective tissue, and that many of the apocrine glands had their lumen distended with leucocytes.

The pathogenesis of this condition is still unknown, and there is a lack of evidence to support the original concept of hidradenitis suppurativa being primarily a disease of apocrine glands. No

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significant differences have been found in the size and density of the aprocrine glands in hidradenitis suppurativa compared with normal controls.[5] It has been postulated that the initiating event in the disease is occlusion of the apocrine duct orifice. Some support for this comes from keratinous plugging of the apocrine duct produced in the axillae of 12 normal male subjects by the application of perforated belladonna adhesive tape to manually depilated axillary skin.[6] Three of the 12 subjects developed lesions at the tape sites which clinically resembled hidradenitis suppurativa. However, this study may not represent an appropriate model for the disease.

Hidradenitis suppurativa may also be seen in association with other conditions where occlusion of follicular structures plays a more obvious role, namely acne conglobata and dissecting folliculitis of the scalp. These three conditions have been referred to collectively as the 'follicular occlusion triad'. More recently another component, pilonidal sinus, has been added to form a 'tetrad'.[7]

In order to gain more information about the pathogenesis of hidradenitis suppurativa, a retrospective study was made of the histology in axillary skin from patients with this condition.

METHODS

Specimens of axillary skin surgically excised from 12 patients with clinically established hidradenitis suppurativa were examined. The tissue was fixed in 10% formol saline and processed routinely. Serial sections 4-μm in thickness were cut and stained with haematoxylin and eosin. The histological features were compared with control specimens of post-mortem axillary skin obtained from 10 cadavers with no previous history of hidradenitis suppurativa or other dermatological problems and with axillary skin surgically excised from one patient with hyperhidrosis. Particular attention was paid to the type and distribution of inflammatory changes in the skin, and to morphological abnormalities of the sweat glands and the pilosebaceous units. In cases where the inflammatory infiltrate was dense and the sweat glands difficult to recognize on haematoxylin and eosin-stained sections, an immunoperoxidase stain for cytokeratin CAM 5.2 was used. This delineates the sweat glands clearly from the surrounding structures, and the eccrine glands show a more intense and uniform staining than the apocrine glands, providing an additional means of distinguishing them, even in the presence of severe inflammation.

RESULTS

In specimens from 10 out of 12 patients with hidradenitis suppurativa, cystic structures lined by stratified squamous epithelium and containing laminated keratin were identified in the dermis (Fig. 1). Half of these contained free hair shafts, suggesting that they represent abnormal dilated hair follicles (Fig. 2). In four cases, there were also epithelium-lined sinus tracts extending directly from the surface epidermis into the deep dermis. Axillary skin from one of the patients contained a cyst lined by squamous epithelium with some adjacent eccrine glands but no apocrine glands. In all the specimens, the apocrine glands showed no significant morphological abnormalities.

Skin from all the patients exhibited chronic inflammatory changes with extensive scarring in the dermis and subcutis. Acute inflammation was also present in eight of the 12 cases. However, in specimens from seven patients, there was no inflammation in apocrine glands, despite inflammatory cells being identified around hair follicles and the epithelium-lined cysts and

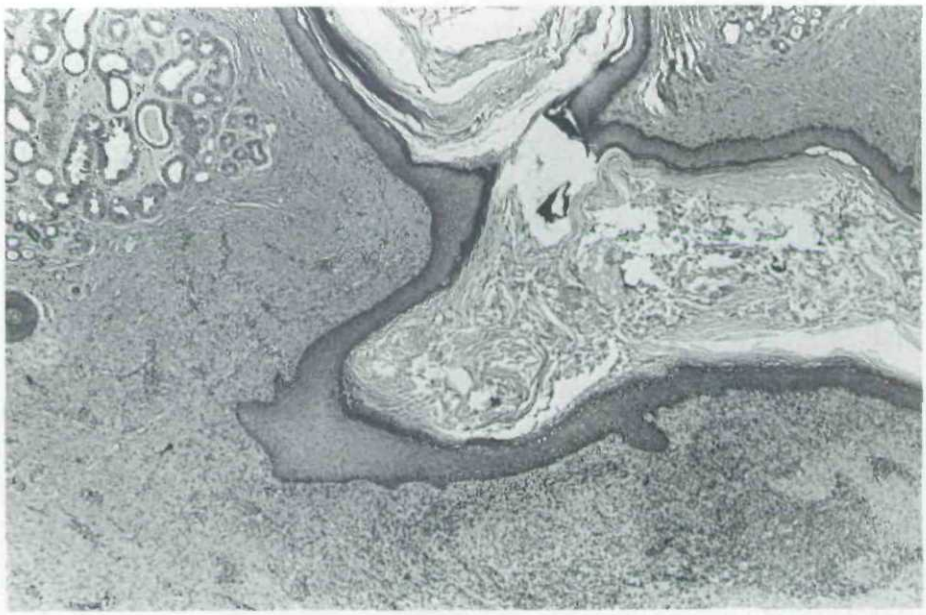

FIGURE 1. Axillary skin showing irregular epithelium-lined structure in a case of hidradenitis suppurativa. The inflammatory cell infiltrate is most intense adjacent to the squamous epithelium (bottom of picture) and peri-follicular scarring is prominent (particularly on the left). The apocrine sweat glands appear normal (top left and right). (H & E × 32)

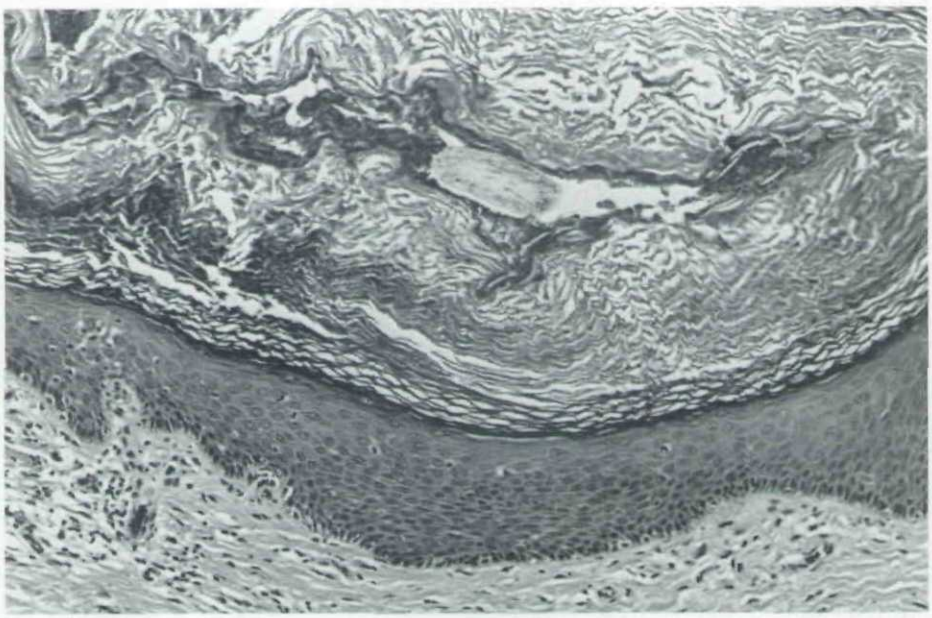

FIGURE 2. Laminated keratin and hair shaft seen within one of the cystic structures in axillary skin. (H & E × 125).

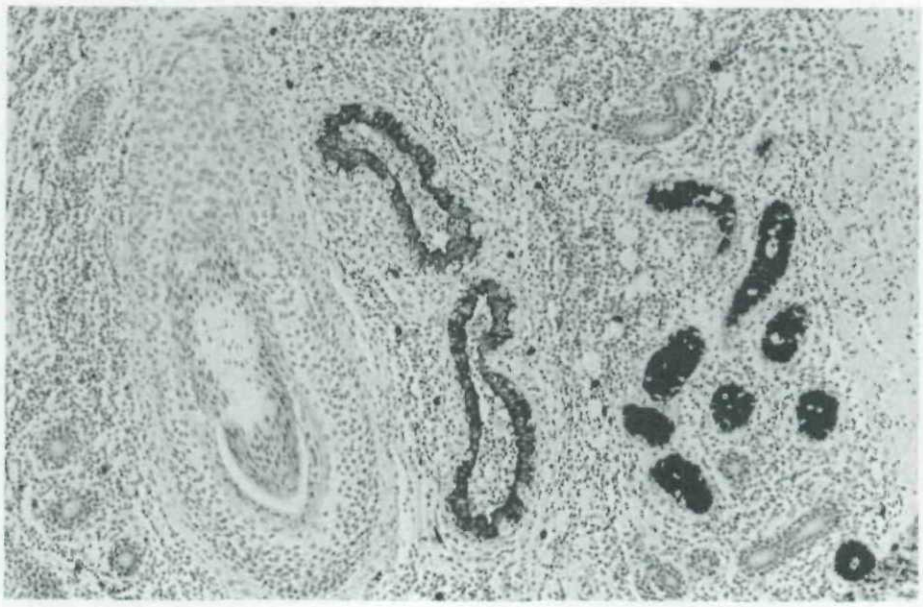

FIGURE 3. A case with extensive inflammation involving not only the apocrine glands (in the centre of the field) but also eccrine glands (on the right) and a hair follicle (to the left). (CAM 5.2 × 80).

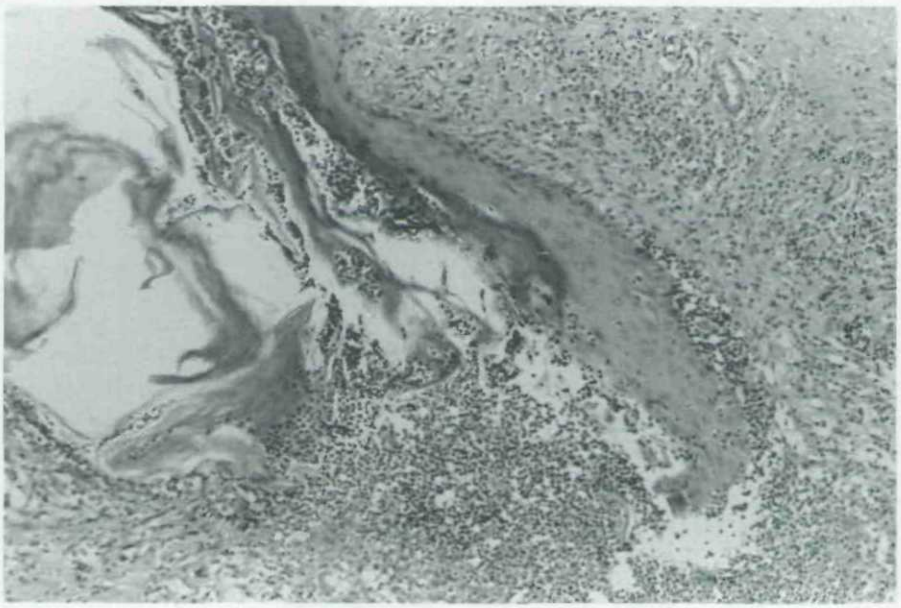

FIGURE 4. A dense infiltrate of neutrophils around the disrupted follicular epithelium (H & E × 80).

TABLE 1. Histological features in hidradenitis suppurativa (total number of patients = 12)

Feature	No. patients affected
Cystic epithelium-lined structures (5/10 with disruption of epithelium)	10
Sinus tracts lined by squamous epithelium	4
Chronic inflammation and scarring	12
Acute inflammation	8
No inflammation in apocrine glands	7
Extensive inflammation (involving all dermal and appendageal elements)	4

tracts described above (Table 1). In four cases, inflammatory changes did involve apocrine glands, but in these the inflammation was extensive and was also present around other structures, including eccrine glands, hair follicles and the cystic structures (Fig. 3). None of these cases showed inflammation centred preferentially around the apocrine glands. In contrast, five of the 10 cases with 'cysts' displayed discontinuity of the squamous epithelium lining these structures, suggesting ulceration or rupture, and in these sections, the inflammatory infiltrate was most intense around the disrupted epithelium (Fig. 4).

DISCUSSION

The histopathological findings suggest that squamous epithelium-lined structures, taking the form of cysts or sinuses, are a more consistent diagnostic feature of hidradenitis suppurativa (being present in 10 out of 12 cases) than inflammation of apocrine glands (found in only four out of 12 cases). The presence of hair shafts within these structures supports the view that they are abnormal dilated hair follicles. This is in agreement with the view that hidradenitis suppurativa is a disease of 'follicular occlusion', rather than a primary 'apocrinitis'. The inflammation seen in these cases did not seem to involve the sweat glands more than other neighbouring structures. However, where the epithelium-lined structures showed evidence of rupture, the inflammatory cells did appear to be most densely distributed at these sites. A review article on hidradenitis suppurativa stated that dilatation of the apocrine gland was a feature and that this eventually led to rupture of the gland with spread of the infection to adjacent apocrine and eccrine glands.[8] In no case were we able to demonstrate gross dilatation of the apocrine glands or any discontinuity of the cells lining the glands or their ducts. The ruptured cysts in our cases had a lining of stratified squamous epithelium similar to the epidermis and the epithelium lining hair follicles.

Although the work of Shelley and Cahn[6] mentioned above has frequently been quoted in the literature as an experimental model for hidradenitis suppurativa, it may not be an accurate model for a number of reasons. Manual depilation of the skin is a traumatic procedure and may produce changes in hair follicles and surrounding tissues, in the same way that shaving skin with a safety razor has been shown to predispose to infection.[9] The addition of atropine to the tape which was applied to the axillae of the subjects cannot be regarded as simulating a physiological

process. Also, lesions clinically resembling hidradenitis suppurativa were produced in only 25% of the patients. Other investigators[10] have pointed out that the acute lesions induced have not progressed to the chronic condition recognized as hidradenitis suppurativa. Histological examination of axillary skin from the three positive cases of Shelley and Cahn showed keratinous plugging of dilated apocrine sweat ducts and inflammatory changes confined to a single apocrine sweat gland unit. The adjacent glands, hair follicles and eccrine glands appeared entirely normal. We have not seen this, even at the edge of the inflammatory lesions bordering on normal skin, which might have been expected to show the early changes of hidradenitis suppurativa.

Further evidence that occlusion of the apocrine duct orifice is not involved in the pathogenesis of hidradenitis suppurativa comes from comparison with Fox-Fordyce disease. This condition presents as a chronic papular eruption associated with pruritus, in areas containing apocrine glands. Histological examination of skin from these patients shows follicular plugging in the epidermis with occlusion of the orifice of the apocrine ducts. The continued secretion of sweat leads to rupture of the duct and the formation of aprocrine sweat retention cysts.[11] The follicular plugging in this condition produces specific changes in the apocrine glands, yet the clinical and pathological features of this disease are distinct from those of hidradenitis suppurativa.

The pathological features of hidradenitis suppurativa that we have observed bear many similarities to those of acne. The epithelium-lined structures resemble comedones.[12] In a review of a large series,[13] 70% of patients with hidradenitis had active acne or evidence of past acne. Hidradenitis suppurativa is distinguished by its peculiar distribution, and by chronic relapsing inflammation, which is difficult to manage both medically and surgically. The predilection of this disease for particular anatomical sites corresponds not only to the distribution of apocrine glands in the body, but also to the distribution of terminal hair follicles dependent on low concentrations of androgens. Hidradenitis may be considered as a suppurative inflammation of these terminal hair follicles, with their associated apocrine, eccrine and sebaceous glands being secondarily involved. Acne is a disease of sebaceous follicles, but the fundamental change in both conditions may be similar, i.e. hyperkeratosis of follicular epithelium leading to formation of comedo-like structures. The bacteriology of acne is characteristic, *Propionibacterium acnes* being found in virtually all comedones,[12] and there is evidence for this micro-organism being the mediator of comedo rupture, which leads to inflammation. In hidradenitis suppurativa, a wide variety of different bacteria have been isolated,[14] but not *P. acnes*. Treatments in acne vulgaris have not been uniformly effective in hidradenitis suppurativa and antibiotics do not produce any long-term remission. The results of treatment with isotretinoin have at best been equivocal, although therapy with the anti-androgen cyproterone acetate appears to be more successful.[15,16]

In our histological review, inflammation of the apocrine glands does not appear to be a primary feature of hidradenitis suppurativa, or a useful diagnostic feature. These findings agree with those of Plewig and Steger,[17] who have used the term 'acne inversa' to encompass hidradenitis suppurativa, as well as the other diseases in the follicular occlusion triad and tetrad. This concept takes into account the similarities, as well as the differences, between these conditions and acne.

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