Differentiating neoplasms of hair germ¹

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SYNOPSIS Differentiating neoplasms of hair germ are benign epithelial-mesenchymal tumours of skin in which hair follicle development may be partly or completely recapitulated. The epithelial component is equivalent to the hair germ. The mesenchymal component is equivalent to the dermal papilla. Epithelial-mesenchymal interaction results in the morphogenesis of hair follicles. In neoplasms showing stromal induction, there is centrifugal organization: hair bulbs are found at the periphery of tumour lobules and hairs are projected centrally to lie within small keratinizing cysts. Neoplasms of hair germ without advanced morphological differentiation are termed 'trichoblastomas', and those neoplasms in which hair follicle development is advanced are called 'trichogenic trichoblastomas'.

This report describes a small group of unusual cutaneous neoplasms, probably derived from hair germ, which (1) recapitulate the development of the hair follicle; (2) illustrate an inductive relationship between epithelial and mesenchymal components analogous to that between hair bulb and dermal papilla; (3) demonstrate a topographical organization similar to that seen in the skin; and (4) do not correspond to neoplasms previously described.

Material

Two of the three neoplasms (cases 1 and 2) were obtained from the files of the Department of Pathology in The University of Michigan; the third was acquired through the courtesy of Professor Tawan Virayakul, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Pertinent clinical details are given in the Table.

Methods

Sections stained with haematoxylin and eosin were available from case 1 and 2; the paraffin blocks were also available from case 1. In case 2 the entire neoplasm, fixed in 10% neutral buffered formalin and embedded in paraffin, was available. Special stains for reticulin (Wilders), elastic fibres (Verhoeff's), glycogen (PAS with and without malt diastase digestion), hyaluronic acid (alcian blue with and without bovine testicular hyaluronidase digestion), and acid mucopolysaccharide (colloidal iron technique of Hale as modified by Rhinehart and Abdul-Haj) were used on the material from cases 1 and 3. In case 3 serial sections to depict topographical relationships were cut and stained from selected blocks.

Case No.	Age	Sex	Site	Comment
1	31	F	Scalp	No recurrence, 4 yr
2	25	F	Buttock	Onset at puberty
3	51	M	Groin	Asymptomatic progressive growth, 1 yr

Table *Clinical data on cases of neoplasm of hair germ*

Received for publication 9 February 1970.

¹Presented in part at the annual meeting of the International Academy of Pathology, on 11 March, 1968, San Francisco, California.

Clinical and Gross Findings

CASE 1

A raised, broadly pedunculated hairless mass, $1.7 \times 1.5 \times 0.5$ cm, was present in the scalp. Small cystic areas were noted in the substance of the neoplasm after it was sectioned.

CASE 2

The lesion consisted of focal thickening and small yellow prominences in the skin overlying a subcutaneous lobular mass. The largest of the lobules was within the subcutaneous panniculus and did not appear to be directly attached to the dermis. The colour and consistence of this neoplasm were not recorded. It exceeded 1.0 cm in diameter.

CASE 3

The neoplasm was $5.0 \times 3.0 \times 2.0$ cm. There was no attached skin or subcutaneous tissue. The surface was grey-white, firm, and slightly bosselated; a few delicate strands of connective tissue adhered to it. The cut surface was white, hard, and vaguely convoluted. There were no areas of softening and no cysts.

Significant gross features of these neoplasms are that all are longer than 1.0 cm in the greatest dimension; all are found within the dermis or the junction of dermis and subcutaneous tissue and two of three tumours were removed as discrete lobular masses.

Microscopic Findings

CASE 1

The lesion was well circumscribed and entirely intradermal. The expansile growth of the mass had displaced sweat glands and pilosebaceous units and caused thinning of overlying epidermis. Most of the neoplasm was formed by discrete and confluent nodules of epithelial cells contained within a loose-textured fibroblastic stroma (Fig. 1). Two general configurations of epithelial elements were found: (a) well defined, circumscribed anastomosing masses of epithelial cells, frequently arranged in double-celled strands, and closely associated with collagen-forming stroma (Fig. 2), and (b) nodular aggregates

Fig. 1 Case 1. Trichoblastoma. Low-power view shows solid islands of uniform epithelial cells and contrasting anastomosing strands of epithelial cells, some organized in a distinct double row. Stroma is more dense in association with epithelial strands. H & E, $\times 75$.

Fig. 2 Case 1. Trichoblastoma. Higher-power view of the tumour shown in Figure 1. A uniform ball of small polygonal cells showing a distinct peripheral palisade is in continuity with double-cell epithelial strands. The pattern closely resembles a hair bulb without a dermal papilla. H & E, $\times 125$.

Fig. 3 Case 1. Trichoblastoma, the structure simulating hair bulb. Note uniformity of matrix-like cells and dark masses of melanin pigment. In contrast to areas anastomosing cell cords, stroma is not prominent. H & E, $\times 275$

Fig. 4 Case 2. Trichogenic trichoblastoma. Low-power view shows a lobular pattern, dense cellular stroma, and central epidermal microcyst. Note that epithelial strands are confined by a thick stromal envelope. H & E, $\times 40$.

small, uniform polygonal epithelial cells often containing abundant melanin pigment (Fig. 3). These epithelial cell cords and nodular masses were occasionally in continuity with each other. Some of the largest epithelial nodules had undergone central liquefactive necrosis with microcyst formation.

The anastomosing epithelial strands closely resembled hair germ of the catagen follicle (Fig. 1), and the solid masses of small polygonal cells hair matrix (Figs. 2 and 3). There was, however, no evidence of hair follicle morphogenesis or incomplete organization of 'matrices'.

A paraepithelial fibroblastic stroma was present between some anastomosing epithelial cords but did not increase in density around nodular epithelial masses. Compared with normal dermis, the interstitial acid mucopolysaccharide content was slightly increased in the fibroblastic areas. The stromal-epithelial masses appeared randomly distributed without any suggestion of topographical organization or lobular configuration.

This lesion (trichoblastoma) was considered to be an example of a neoplasm of hair germ in which stromal induction had resulted in the

formation and organization of matrix-like cells but in which hair follicles had not developed.

CASE 2

The general configuration was that of a well-circumscribed nodular mass surrounded by delicate collagenous envelope. Lobules were composed of anastomosing strands of epithelial cells, often in a double row, enclosed by moderately cellular fibroblastic stroma with variable collagenization. Epithelial elements were not observed at the periphery of the neoplasm; the outermost zone was always composed of collagenous stroma. In the peripheral zone, epithelial cords usually paralleled the margin of the lobules (Fig. 4).

Within some lobules, islands of matrix cells showed various degrees of organization, frequently forming abortive hair follicles containing central keratohyaline masses (Fig. 5). When such follicle-like structures developed, the peripheral epithelial cells also showed differentiation and organization to simulate the outer hair sheath (Fig. 5). On such abortive follicle clearly duplicated a dermal

Fig. 5 Case 2. Trichogenic trichoblastoma. Components of an abortive hair follicle are present, including focal development of the clear cells of the outer sheath. Note continuity with anastomosing epithelial strands and cellular paraepithelial collagenous stroma. H & E, $\times 125$.

Fig. 6 Case 2. Trichogenic trichoblastoma. Note a well formed bifid hair bulb and double papilla. Clear cells of the outer sheath are in continuity with the bulb. H & E, $\times 140$.

Fig. 7 Case 2. Trichogenic trichoblastoma. A small epidermal cyst consistent with ectatic hair sheath contains well formed hairs. H & E, $\times 140$.

papilla with a bifid bulb (Fig. 6). Within a few lobules small cysts lined by keratinizing squamous epithelium contained well formed hair shafts (Fig. 7).

Topographical organization of the lobules was manifested by (1) epithelial components of lobules always circumscribed by more peripheral stromal elements; (2) hair follicle morphogenesis tending to occur toward the periphery of the lobules where almost all well formed follicles were found; (3) hair shafts, when formed, always projecting towards the centre of the lobule. Such hair shafts were always enclosed within epithelium; none were found outside the collagenous envelope of the neoplasm and no foreign body reaction to hair shafts was seen within the neoplasm.

This lesion (trichogenic trichoblastoma) was interpreted as a neoplasm of hair germ with advanced stromal induction, in which both true follicles and follicle-like structures were formed.

CASE 3

This neoplasm consisted of anastomosing lobules similar in configuration to case 2. Stromal-epithelial masses were surrounded by loosely organized vascular connective tissue which

Fig. 8 Case 3. Trichogenic trichoblastoma. Low-power view shows a dense peripheral stromal mantle and cross-cut hair follicles at various levels. Anastomosing epithelial cords are found within ill-defined lobules. Note blood vessels within an interlobular system at the arrow. H & E, $\times 40$.

Fig. 9 Case 3. Trichogenic trichoblastoma. A small hair follicle with its base toward the periphery of a lobule is in continuity with epithelial cords. Note the delicate reticulin pattern adjacent to epithelium. Reticulin, $\times 80$.

Fig. 10 Case 3. Trichogenic trichoblastoma. Higher power view of the epithelial area seen in Figure 8. The cellular paraepithelial stroma is rich in AMP and contains numerous mast cells. H & E, $\times 120$.

penetrated between the lobules (Fig. 8). Large thin-walled blood vessels formed an interlobular plexus, while smaller vessels penetrated the lobules.

The intralobular connective tissue was more dense and collagenized toward the periphery of the lesion; adjacent to epithelial cords it was loose-textured and more cellular. This paraepithelial zone was rich in hyaluronic acid and contained moderate numbers of mast cells, contrast to small numbers in the dense peripheral stroma.

Delicate reticulin fibres were found in the greatest number in the paraepithelial zones, and increased in number where epithelial cells were palisaded to replicate outer hair sheath. The reticulin adjacent to epithelial cords also showed a tendency to orientate perpendicular to epithelial basement membranes. Small numbers of elastic fibres, without any special pattern or relationship, were found within interlobular stroma.

Although well developed hair follicles were found in several lobules (Figs. 8 and 9), most of the neoplasm contained only interconnecting epithelial cords similar to those described in case 2 (Fig. 10).

Topographical organization of this neoplasm, although subtle, was definite and precise. The pattern was similar to that described for case 2. Most follicles were orientated with their dermal papillae to the periphery and their apices toward the centre of the lobules. Hair shafts sheathed

Fig. 11 Case 3. Trichogenic trichoblastoma. Low-power view shows a small epidermal cyst containing dense adherent keratin masses. The cyst is in continuity with epithelial strands. In serial sections, hairs were projected into such cysts. H & E, $\times 30$.

epithelium projected within small cysts lined by keratinizing squamous epithelium (Fig. 11). Several areas of the epithelium adjacent to and continuous with the epithelium of small cysts receiving projected hairs showed unmistakable sebaceous differentiation (Fig. 12).

This lesion (trichogenic trichoblastoma) was interpreted as a benign neoplasm of hair germ showing advanced focal morphogenesis as well as topographical organization.

The complete microscopic features of tumours showing advanced stromal induction are summarized as follows:-

1 Sharply circumscribed stromal-epithelial masses form interconnecting lobules.

2 The peripheral margin of a lobule is invariably stromal. The stroma becomes more cellular and increases in the interstitial acid mucopolysaccharide content adjacent to epithelium.

3 The undifferentiated epithelial component consists of anastomosing epithelial cords which frequently line up in a two-cell column or row.

Fig. 12 Case 3. Trichogenic trichoblastoma. Areas of sebaceous differentiation of epithelium in continuity with a cyst wall similar to that shown in Figure 11. H & E, $\times 275$.

4 Differentiating hair follicles are found in continuity with epithelial cords.

5 When hair follicles are formed, there is a tendency for hair bulbs to be orientated to the periphery and for hairs to be projected towards the centre of the lobule.

6 Hairs originating from completely developed follicles are usually contained within epithelial sheaths until they project into small cysts lined by keratinizing squamous epithelium.

7 Focal sebaceous differentiation may be present.

Discussion

During catagen of the normal cycle of hair loss and regrowth the definitive hair germ is a cord of undifferentiated epithelial cells which extends from the remnants of the outer sheath to the dermal papilla (Montagna and Van Scott, 1958). During anagen, hair germ organizes and differentiates into hair matrix which then forms hair shaft, hair cuticle, and the various layers of the inner sheath. Because the hair bulb is lost with the onset of catagen, the germinative source of each

new generation of hair follicles must originate from the epithelial extension of the outer sheath to dermal papilla, the hair germ.

In this study, while there is not direct morphological evidence that the epithelial cords found in each of the neoplasms described is actually hair germ, there is good circumstantial evidence in the form of developing hair follicles in continuity with undifferentiated epithelial cords which closely simulate hair germ, and in the intimate association of epithelium with mesenchyme.

In normal anagen hair follicles the dermal papillae contain abundant metachromatic mucopolysaccharide (Oliver, 1968; Braun-Falco, 1958). The large amounts of acid mucopolysaccharide in the paraepithelial zone of the intralobular connective tissue in these hair germ tumours (case 3) are regarded, therefore, as additional evidence that this mesenchymal zone is analogous to active dermal papillae. The many small capillaries observed within the mucopolysaccharide-rich intralobular connective tissue of the neoplasms are also similar to the highly vascular state of the dermal papilla during the growth phase of the hair follicle.

It is generally regarded that during catagen club hair formation with loss of hair bulb and lower sheath is discontinued distal to the sebaceous gland. The sebaceous gland is not lost and regenerated in cyclic fashion (Montagna and Van Scott, 1958). However, the regeneration of sebaceous glands from cells of the outer sheath has been demonstrated experimentally (Montagna and Chase, 1950), and sebaceous differentiation of epidermal cells has also been noted. The differentiation in one of these neoplasms (case 3) suggests that hair germ neoplasms may, in certain foci, be capable of differentiation as an entire pilosebaceous unit.

Experimental evidence now supports the postulate that the dermal papilla induces hair formation (Oliver, 1968). Additional investigative work has provided evidence for the inductible effects of mesenchyme in the morphogenesis of feathers (Wang, 1943) and teeth (Pindborg and Clausen, 1958). It is therefore central to the concept of differentiating neoplasms of hair germ that the mesenchymal component is essential for the induction of hair follicles from hair germ epithelium. Differentiating neoplasms of hair germ are, therefore, not exclusively epithelial tumours, but are in fact heterogeneous biological systems of epithelial-mesenchymal interaction.

The two hair germ neoplasms in which hair follicles were well developed displayed an unusual degree of topographical organization. If each neoplastic lobule were considered to be a sphere, the bulbs of almost all of the observed hair follicles are in a centrifugal position. Furthermore, these follicles are orientated perpendicular to the surface of the lobule and extend toward the centre. Hair shafts in these lesions do not grow haphazardly into connective tissue; they remain

within epithelial sheaths and project into small cysts lined by keratinizing squamous epithelium which tend to be located toward the centre of the lobules. Thus the natural projection of hair toward an epithelial surface is maintained in the highly differentiated hair germ neoplasms. This tendency for normal cutaneous relationships is also seen in the epithelial areas of benign cystic teratomas of ovary as well as in so-called dermoid cysts in other sites.

In view of the enormous numbers of normal hair follicles within man and beast in which there are many cycles of hair growth, and in view of the intense mitotic activity and biological sensitivity of proliferating matrix cells, it is astonishing that neoplastic aberrations of the hair cycles are not more common. Differentiating neoplasms of hair germ are in fact extremely rare. A survey of all cutaneous adnexal tumours received in the Department of Pathology in the University of Michigan since 1896 has yielded only two examples. A search of the world's literature has revealed no reports, with the exception of case 2 which was previously described in a survey of primary neoplasms of the hair follicle (Headington and French, 1962). At that time this neoplasm was erroneously considered as arising from hair matrix, not hair germ, although the suggestion of its stromal induction was briefly discussed and the obvious relationships and similarities to certain odontogenic neoplasms were commented on.

Two well recognized and commoner lesions deserve comparative comment. The first, trichoeptithelioma (Gray and Helwig, 1963) (epithelioma adenoides cysticum), is a usually benign, well circumscribed epithelial proliferation, occasionally transmitted as an irregular autosomal dominant trait, in which small keratinizing cysts simulating effete hair follicles may be found. Hair, hair matrix cells, and stromal aggregates consistent with dermal papillae are not present. The second lesion, trichofolliculoma (Gray and Helwig, 1962), microscopically has a characteristic pattern of small and frequently well developed follicular structures radiating from a central keratinizing cystic space which is usually in continuity with the epidermis. Well formed dermal papillae and hairs often give the characteristic clinical finding of a tangled tuft of small hairs emerging from the skin surface. The small size, central cystic space, constant intradermal location, and continuity with epidermis serve to distinguish this lesion from the trichogenic trichoblastoma.

The trichomatrioma (Hulett, 1958) (the pilomatricoma, calcifying epithelioma, of Forbiss and Helwig, 1961) is composed of hair matrix cells without evidence of stromal induction.

The description of this small group of differentiating neoplasms of hair germ suggests that a number of interesting morphological variants are possible, and, although rare, they can be separated with confidence from other neoplasms of cutaneous adnexae.

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