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Malignant transformation within benign adnexal skin tumours

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Aims: To report five malignant trichogenic tumours arising in longstanding, previously benign adnexal neoplasms through malignant transformation. Malignant trichogenic adnexal tumours are extremely rare neoplasms.
Methods and results: The patients were between 55 years and 79 years of age. Three of the tumours were located on the arms, two on the face. Three of our patients had a history of chronic lymphocytic leukaemia, one patient had a history of colonic adenocarcinoma. The duration of the tumour nodules was reported as between 20 and 40 years before sudden changes occurred. These changes included rapid growth, pain, itching, ulceration and bleeding. Histologically, all tumours were well circumscribed and encapsulated. There was a residual benign tumour component and morphological signs such as bone formation, dystrophic calcification and sclerosis suggesting long duration of the lesions. All patients except for one, who refused further clinical investigation due to her advanced age of 79 years, had an underlying systemic malignancy.
Conclusions: The growth stimulus in these benign adnexal neoplasms resulting in malignant transformation may be attributed to the acquisition of additional genetic events or to immunosuppression due to an underlying neoplastic disease. Therefore, patients with systemic diseases or malignancy should be carefully examined and followed for sudden changes in pre-existing benign cutaneous tumours.

Keywords: adnexal carcinoma, carcinosarcoma, CLL, immunosuppression, trichogenic tumours

Introduction

Trichogenic tumours are rare neoplasms and most are benign. Ackerman uses the term 'trichoblastomas' for neoplasms that are constituted mostly of follicular germinative cells[1] but also for a variety of benign trichogenic adnexal tumours which are referred to by others as trichoepithelioma, trichoblastoma, trichodiscoma and trichofibroma. The clinical presentation includes macules, papules, nodules and plaques and the most characteristic feature of all these benign adnexal tumours is their long duration without change. Adnexal tumours arising from the upper segment of the hair follicle such as the infundibulum (trichoadenoma, naevus comedonicus, dilated pore) or isthmus (pilar sheath acanthoma) show keratinization, cornification and horn-filled cysts, whereas those arising from the hair bulb region (trichoblastoma, trichoblastic carcinoma, pilomatrixoma) show differentiation along matrix and germ cells, outer or inner root sheath. However, some tumours arising from the bulb region display no epidermal/trichogenic differentiation.[1] The majority of adnexal tumours arise from the upper portion of the hair follicle.[2] Rarely, a benign adnexal tumour arises from the hair bulb region resulting in matrical tumours reported as melanocytic matricoma[3–5] or trichogerminoma.[6] Malignant trichogenic tumours are exceedingly rare and arise usually *de novo*.[2] Malignant transformation in longstanding benign adnexal neoplasms constitutes a distinct rarity.[7–9] We describe five cases of malignantly transformed trichogenic adnexal neoplasms, which arose from longstanding benign adnexal tumours.

Materials and methods

All formalin-fixed paraffin-embedded tumours were evaluated on haematoxylin and eosin-stained sections.

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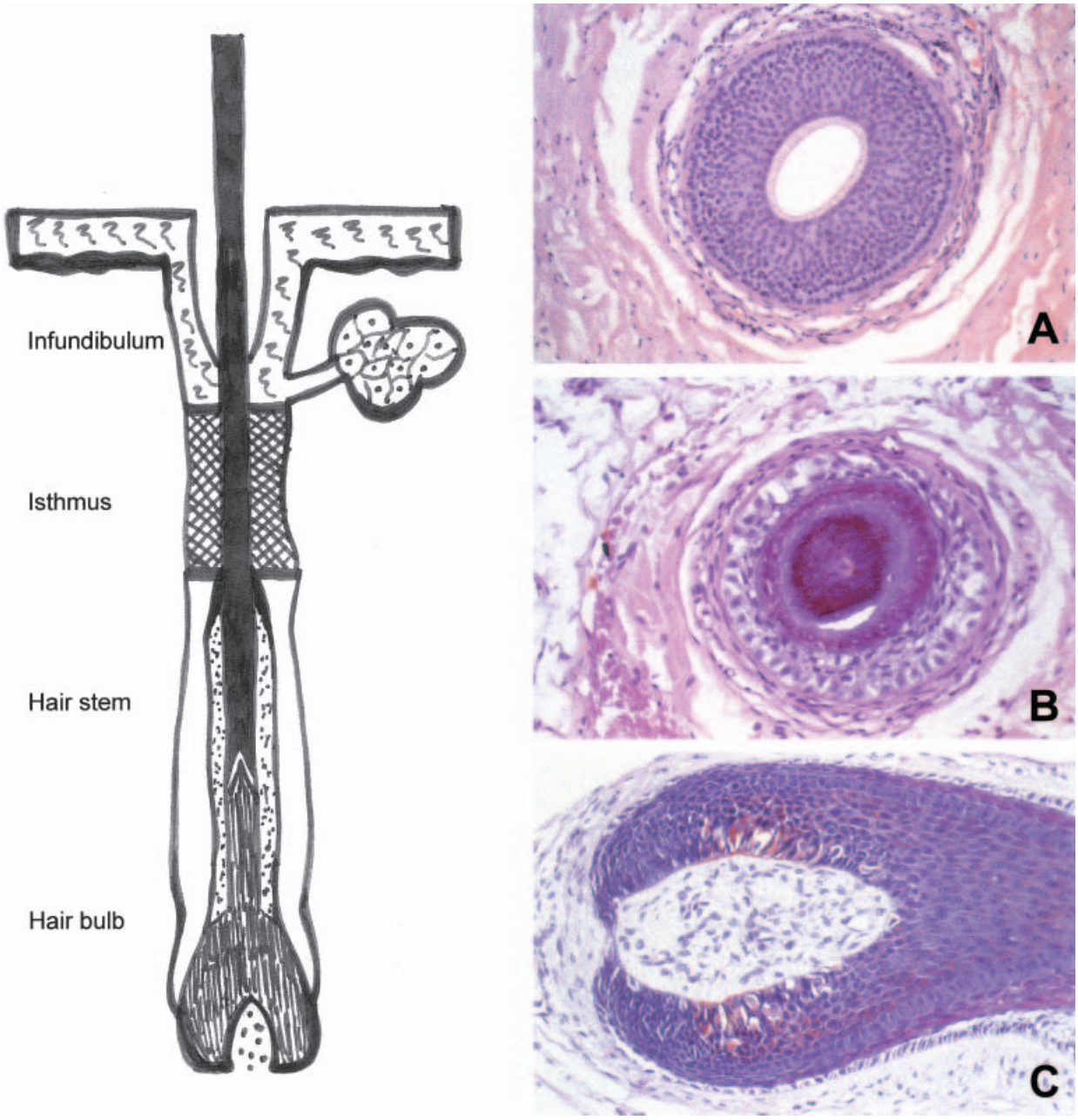


Figure 1. Normal hair histology. **A,** Trichogenic cornification of the ostium, demonstrated in the outer root sheath, is composed of pale clear cells in the bulb area which mature to pink cells in the area of the hair stem. **B,** The inner root sheath is arranged in three layers: the cuticle, the Huxley's and Henle's layer. **C,** The follicular papilla of the hair bulb consists of delicate, fibrillary bundles of collagen, abundant mucin, plump fibrocytes and capillaries. The matrix consists of large round, monomorphous cells with crowded nuclei, prominent nucleoli, stippled chromatin and scant cytoplasm. Note the nuclear palisading and pigment-containing dendritic melanocytes.

Immunohistochemical analysis was performed with antibodies to S100, vimentin, pan-cytokeratin, Ber-Ep4 and to individual cytokeratins (CK)5, 6, 14, 17, and 19 (all antibodies from Dako Corp., Carpinteria, CA, USA) using the streptavidin–biotin complex method, with prior trypsinization or microwave treatment as required. For control purposes, tissues known to contain the respective antigens were included (positive controls). Replacement of the primary antibody by normal serum always led to negative results (negative controls).

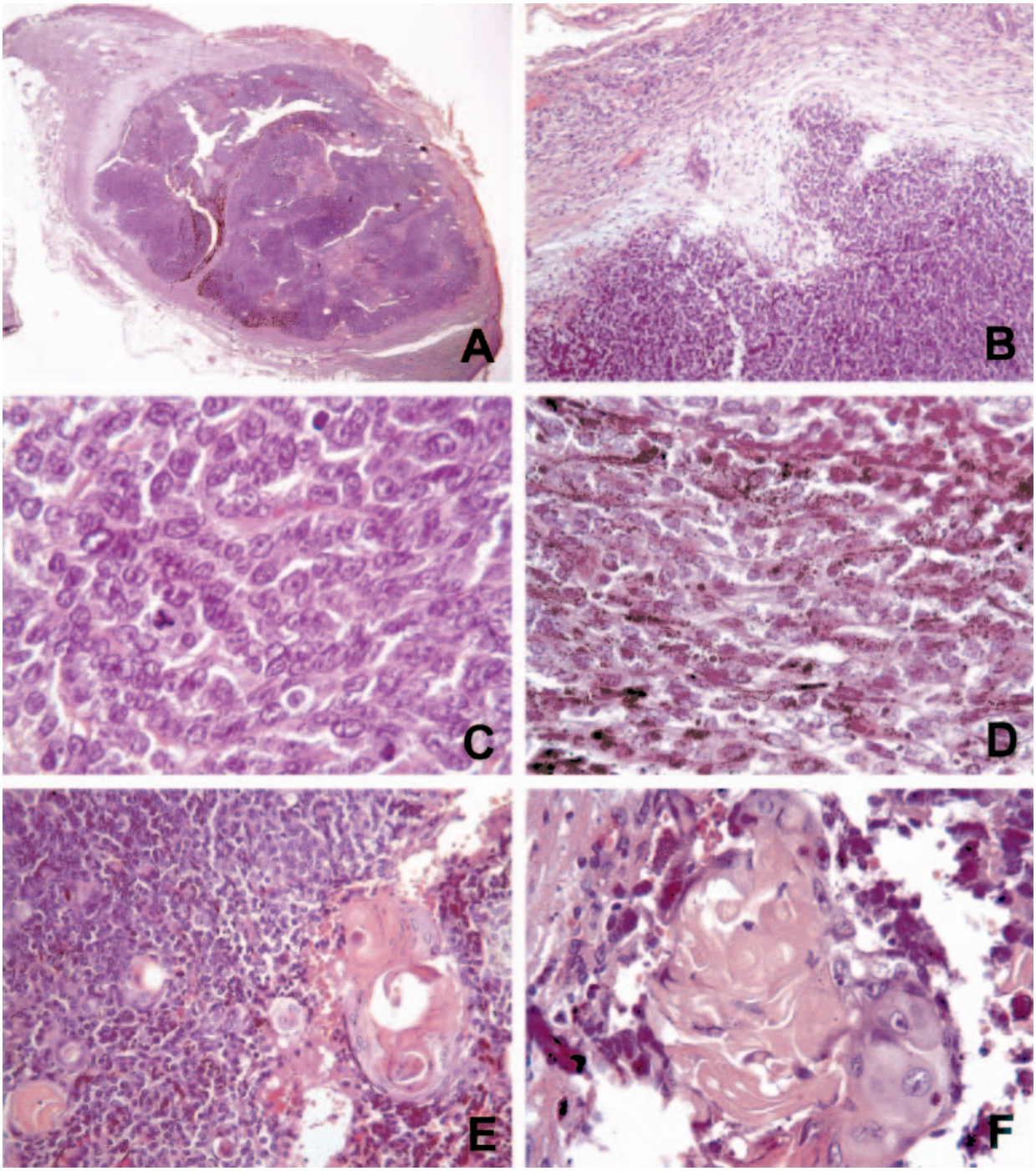


Figure 2. The malignant melanocytic matricoma is a well-circumscribed dermal tumour (**A**) infiltrating the capsule (**B**), consisting of small basaloid uniform cells with numerous mitoses (**C**) and darkly pigmented dendritic melanocytes (**D**). Numerous horn pearls and cysts as well as occasional ghost cells are identified (**E,F**).

Results

NORMAL HAIR HISTOLOGY (FIGURE 1)

For an appropriate interpretation and correct diagnosis of adnexal tumours it is essential to know the histology of the normal hair follicle. The hair follicle is divided into an upper and a lower segment. The upper segment consists of the infundibulum and isthmus, the lower segment consists of the stem and bulb. The hair bulb consists of a papilla and matrix: the

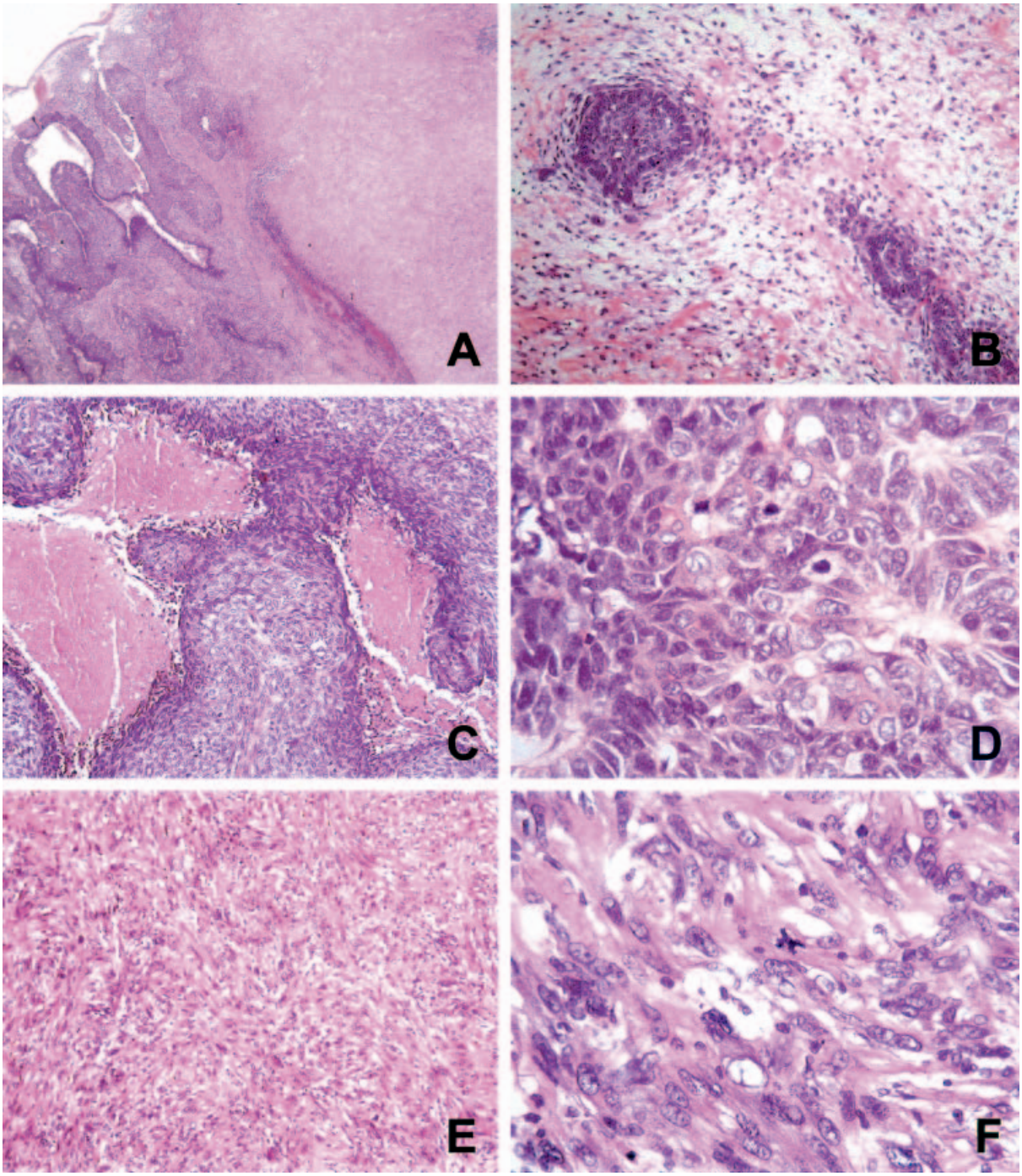


Figure 3. Low-power view of the bi-phasic tumour with a blue epithelial and pink solid mesenchymal component (**A**). The periphery shows benign epithelial proliferations with immature hair buds exhibiting the typical nuclear palisading (**B**). The carcinomatous component shows lobules of basaloid cells with areas of necrosis (**C**). The cells have scant cytoplasm and large hyperchromatic nuclei (**D**). The mesenchymal component is arranged in long intersecting fascicles of spindle cells embedded in a fibrohyaline matrix (**E**). Note the atypical mitosis (**F**).

follicular papilla is shaped like an inverted pine cone and consists of delicate, fibrillary bundles of collagen, abundant mucin, plump fibrocytes and capillaries. The immature epithelial cells of the matrix show scant cytoplasm and large round monomorphous nuclei with prominent nucleoli and stippled chromatin.

Immediately above the papilla the cells show nuclear palisading. Typical for the epithelium of the papilla are numerous mitoses and individual apoptotic cells. Interspersed are strikingly dendritic, pigment-containing melanocytes. The matrical cells mature to polygonal supramatrical cells with prominent nucleoli and differentiate along two separate pathways to the hair itself and the inner and outer root sheaths. Cells of the future hair are positioned at the apex of the papilla; they are surrounded laterally by cells of the inner sheath, which contain trichohyalin granules and are arranged in three layers: the cuticle, the Huxley's and Henle's layer. In the area of the hair stem, trichogenic cornification of the cells is seen. The outer sheath is composed of pale clear cells in the bulb area which mature to pink cells in the area of the hair stem.

Case reports

CASE 1—MALIGNANT MELANOCYTIC MATRICOMA

A 69-year-old woman with a history of a poorly differentiated colonic carcinoma (pT3), treated with surgery and chemotherapy, presented with a 12-mm solitary, asymmetrical, pigmented papule on the dorsum of the hand. The well-circumscribed dermal tumour extended into the subcutis, and the surrounding fibrous capsule was infiltrated multifocally by tumour cells (Figure 2A,B). The tumour consisted of a dual cell population: (i) basaloid small uniform cells with large round to oval nuclei, stippled chromatin, prominent nucleoli and scant cytoplasm corresponding to matrical and supramatrical cells (Figure 2C), and (ii) darkly pigmented dendritic melanocytes as typically seen in the hair bulb (Figure 2D) with brisk mitotic activity, including atypical mitoses (Figure 2C). Intermixed in both populations were numerous horn pearls and cysts (Figure 2E) as well as ghost cells (Figure 2F). Calcification was not identified. The tumour was interpreted as a melanocytic matricoma. The increased proliferative activity with atypical mitoses and the infiltration of the capsule were considered as evidence for malignant transformation within this tumour. The immunohistochemical analysis with antibodies against S100 showed positivity of the dendritic melanocytes, the epithelial cells stained focally with antibodies to CK6, 17 and 14.

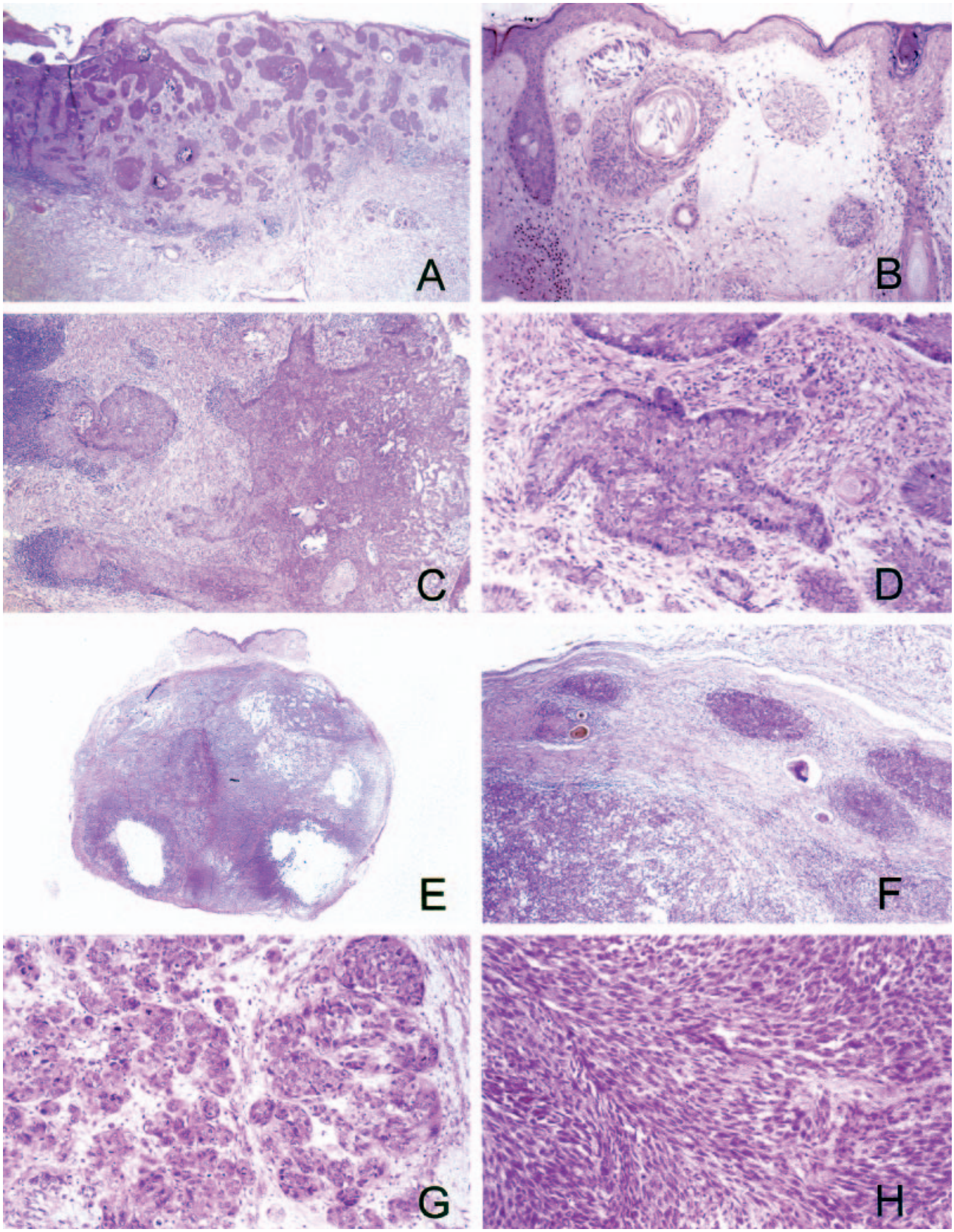
CASE 2—MALIGNANT BIPHASIC TRICHOGENIC TUMOUR (CARCINOSARCOMA)

A 79-year-old woman presented with a 100-mm exophytic tumour on the right cheek. This tumour arose in a flat 50-mm plaque which had been unchanged for 28 years before it began to grow rapidly 1 year before clinical presentation. The patient suffered from severe anaemia, but she refused further clinical work-up. Histological examination showed a dermal, poorly circumscribed and widely invasive tumour with a biphasic carcinomatous and sarcomatous component (Figure 3A) surrounded by benign epithelial proliferations showing adnexal differentiation such as immature hair buds and abortive budding papillae (Figure 3B). The epithelial component showed large areas of necrosis (Figure 3C). The basaloid tumour cells with scant cytoplasm and large hyperchromatic nuclei had brisk mitotic activity with eight mitoses/high-power field (40 × HPF) (Figure 3D). The mesenchymal component was arranged in long intersecting fascicles of spindle cells embedded in a fibrohyaline matrix (Figure 3E). The cells were pleomorphic with vesicular to oval nuclei, coarse chromatin and prominent nucleoli. Multiple typical and atypical mitoses, on average 5/HPF, were counted (Figure 3F). Cysts and horn pearls were not identified. The benign and malignant tumour component consisting of matrical cells showed a positive reaction with Ber-Ep4. Antibodies to cytokeratin stained only the carcinomatous component while vimentin was expressed by the sarcomatous component.

CASE 3—TRICHOGENIC CARCINOMA

A 52-year-old male with a 5-year history of a B-cell chronic lymphocytic leukaemia (B-CLL) presented with a 20-mm ulcerated plaque on the left cheek which had been unchanged for 20 years before it began to grow rapidly. The epithelial tumour arising from the epider-

Figure 4. Case 3: Low-power view of a plaque-like epithelial proliferation centred around hair follicles (**A**). A high-power view of the peripheral benign trichoepithelioma with horn cysts and calcifications (**B**). The central portion shows solid tumour lobules consisting of undifferentiated small blue cells surrounded by nodular infiltrates of lymphocytes consistent with B-cell chronic lymphocytic leukaemia (**C**). The abortive hair bulbs demonstrate peripheral nuclear palisading (**D**). Case 4: The circumscribed dermal tumour consists of proliferations of germinative follicular cells, calcification and cystic structures (**E**). A typical trichoblastoma with nodules of follicular germinative cells, infundibulo-cystic structures and dystrophic hairs is identified in the periphery (**F**). Malignant transformation occurs around pre-existing trichogenic structures in two patterns: tightly packed cell nests (**G**) and sweeping fascicles (**H**).


A
B
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mis consisted of a plaque-like benign adnexal tumour (Figure 4A) with germinative follicular cells and cystic structures; areas of calcification were identified (Figure 4B). The central tumour portion showed a carcinomatous proliferation of undifferentiated small blue cells surrounded by a nodular lymphocytic infiltrate consistent with a B-CLL (Figure 4C). The tumour showed abortive hair bulb differentiation with peripheral nuclear palisading and numerous mitoses (Figure 4D).

CASE 4—MALIGNANT BIPHASIC TRICHOGENIC TUMOUR (CARCINOSARCOMA)

A 55-year-old male with a B-CLL presented with a 35-mm nodule in the deltoid region above the elbow of the right arm. It had been present unchanged for 40 years. The well-circumscribed tumour was located in the deep dermis and subcutis without connection to the epidermis (Figure 4E). The peripheral portions of the tumour consisted of a typical trichoblastoma with small nodules of follicular germinative cells, infundibulo-cystic structures with melanin-containing dystrophic hair and corneocytes (Figure 4F). Extensive dystrophic calcification, granulomatous foreign body giant cell reaction, osteoid deposition and bone formation were also identified. Malignant transformation occurred multifocally as tightly packed nests arising around pre-existing trichogenic structures and spindle cell proliferations in sweeping fascicles (Figure 4G,H). The patient died of widely metastatic disease in axillary lymph nodes, liver and lung. A detailed description of this case is presented.[7]

CASE 5—PILOMATRIX CARCINOMA

A 76-year-old female with a 8-year history with of B-CLL presented with a 20-mm nodule of the forearm close to the elbow of the right arm, which had been present for at least 10 years. The well-circumscribed tumour was located in the dermis without connection to the epidermis (Figure 5A). A significant portion of the carcinoma was calcified (Figure 5B). The carcinoma infiltrated the capsule at multiple sites and extended focally into the deep reticular dermis and subcutaneous adipose tissue (Figure 5A,C). The carcinoma was composed of blue cells with brisk mitotic activity (Figure 5D) and including atypical mitoses (Figure 5E). Calcification and ghost cells were prominent, the stroma sclerotic and amyloid-like. Occasionally, individual pigment-containing cells and melanocytes were encountered (Figure 5E,F). The tumour was interpreted as a pilomatrix carcinoma.

Discussion

Headington was the first to draw attention to what he called a 'group of benign cutaneous neoplasms in which hair follicle development may be partly or completely recapitulated' and called them 'hair germ tumours'.[10,11] These tumours showed an inductive relationship between epithelial and mesenchymal components analogous to hair bulb and dermal papilla, with a topographical organization similar to that seen in the skin. Depending on the combination of epithelial and mesenchymal components and the amount of 'stromal induction', he classified these neoplasms into two groups: epithelial and mesenchymal.[10–12] However, most benign trichogenic tumours consist of varying portions of both components, often with the mesenchymal component being quite scant. In accordance with the dominating epithelial components, two of our cases exhibited only a carcinomatous transformation. One of these two trichogenic tumours was heavily pigmented and consisted of a dual cell population of epithelial cells and melanocytes with an intimate relationship between follicular epithelium and melanocytes.[3,13] The pigment of trichogenic epithelial tumours arising from the bulb region is imparted by the presence of melanocytes which constitute an integral tumour component. The follicular matrix is populated by large melanocytes with long dendrites containing large, almost giant, melanin granules that impart colour to the hair. Melanogenically active melanocytes within bulbar epithelium can only be detected in the anagen stage of the hair cycle. In contrast, epithelial tumours arising from the interfollicular epidermis or infundibular regions of the hair follicle such as seborrheic keratosis and squamous/basal cell carcinomas are thought to be pigmented as a result of increased melanin transfer due to secondary colonization of the neoplasm by melanocytes. Two of the present cases also had a sarcomatous tumour component reminiscent of the follicular papillae which is another strong indicator for an origin from the hair bulb region.

Malignant trichogenic adnexal tumours are extremely rare neoplasms, and are typically described as arising *de novo*. Our cases developed in benign adnexal neoplasms which had been present for many decades. It is not clear what triggers the malignant transformation in previously benign tumours of such long duration. Oncogenesis in this specific setting depends most likely on a change in the host immune surveillance due to malignant lymphoma, B-CLL and post-transplantational immunosuppression.[14–16] Particularly interesting is a very similar case of pilomatrix carcinoma arising on the forearm of

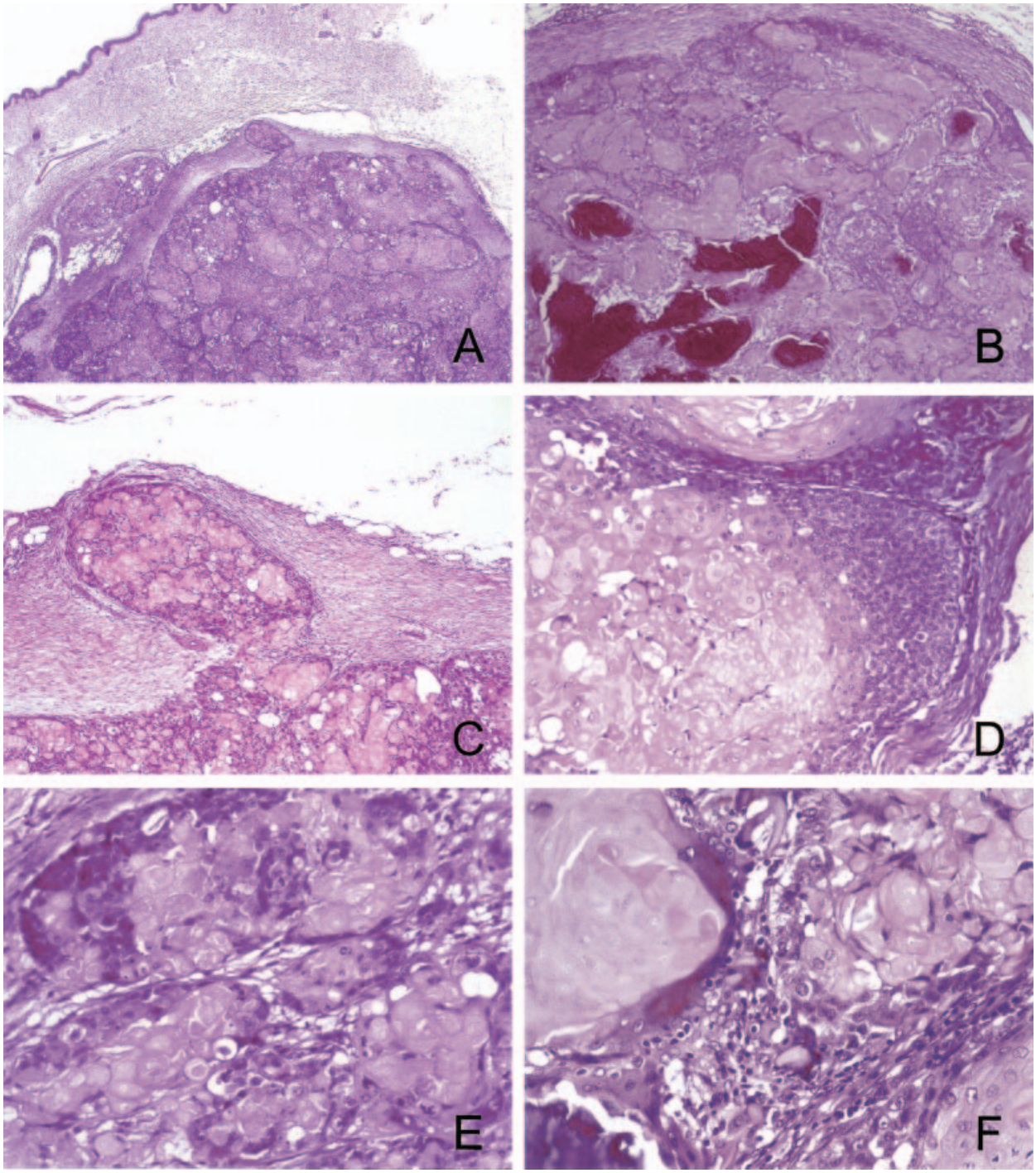

Figure 5. The pilomatrix carcinoma is a well-circumscribed dermal/subcutaneous tumour with invasion of the subcutaneous adipose tissues (**A**). A significant portion of the carcinoma is calcified (**B**). The capsule is multifocally infiltrated (**C**). The blue basaloid cells are surrounded by numerous ghost cells (**D**). Atypical mitoses are frequent (**E**). Other areas show shadow cells with cytoplasmic pigment embedded in a sclerotic stroma (**F**).

an immunocompromised man.[17] Additional genetic events such as activation of oncogenes or inactivation of tumour suppressor genes or loss of regulation of apoptosis may contribute to malignant transformation. In four of our cases (one patient refused further clinical investigation), the sudden transformation was

linked to such an event which may also have been the reason for the underlying systemic oncological disease.

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