Follicular squamous cell carcinoma is an under-recognised common skin tumour

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Abstract

Current thinking assumes most cutaneous squamous cell carcinoma arise from the surface epidermis. Uncommon pilar and tricholemmal carcinomas are well recognised and recently authors have drawn attention to uncommon squamous cell carcinoma with predominant follicular infundibular differentiation. In contrast we propose that follicular (infundibular-tricholemmal) squamous cell carcinoma is exceedingly common and can be defined as follows: cytologically malignant tumour, abrupt connections to the epidermis (at follicular infundibula), infundibular and/or tricholemmal differentiation and lacking co-existent Bowen's disease or distinctive clinical-pathological features of keratoacanthoma. Recognition that many cutaneous squamous cell carcinoma are of follicular origin has major implications for differential diagnosis, staging, prognosis, management and future research.

Keywords cutaneous follicular squamous cell carcinoma; differential diagnosis; keratoacanthoma

Introduction

Basal cell carcinoma is the commonest cutaneous malignancy and is considered to arise from undifferentiated germinative cells of the hair follicle.[1] Other malignant follicular tumours are rare and include: pilomatrical carcinoma (hair bulb and inner root sheath differentiation); tricholemmal carcinoma (lower outer root sheath differentiation)[2–9] and malignant proliferating pilar cyst/tricholemmal tumour (upper outer root sheath differentiation).[10,11] Traditionally tricholemmal carcinoma have been characterised by cytologically malignant lesions showing features of lower outer root sheath differentiation as evidence by some or all of the following features: follicular continuity or folliculocentric lobulated growth, discernible basement membrane, subtle peripheral palisading, large central pale to clear cells with distinct cell membranes, abundant PAS positive glycogen, abrupt tricholemmal keratinisation with indiscernible keratohyalin granules, and positive immunohistochemical staining for follicular outer root sheath epithelium (e.g. CK17, NGFR/p75 and CD34 but the latter marker appears to be negative in most reported cases).[2–9,12] Surprisingly malignant transformation of tricholemmoma appears to be exceedingly rare compared with other follicular lesions and because most purported tricholemmal carcinoma lack many of the features listed above it has been suggested that most simply represent clear cell variants of SCC.[8,9,12] In a recent meticulous study Misago et al could only find 2 or 812 SCC that fulfilled most of the diagnostic criteria above for tricholemmal carcinoma (both lacking pre-existing tricholemmoma or CD34 staining).[9]

In 2004 Diaz-Cascajo described a series ($n = 16$) of follicular squamous cell carcinoma (fSCC) that arose predominantly in the sun-exposed, hair bearing skin of the elderly with a preference for males and behaved indolently.[13] Tumours were centred on the hair follicle with abrupt epidermal connections, lacked directly associated bowenoid dysplasia and were often clinically confused with BCC. Apart from being folliculocentric and attached to the surface via follicular infundibula tumours lacked other features of overt follicular differentiation (as seen in tricholemmal carcinoma above).[13]

In 2008 Kossard et al drew attention to under-recognition of infundibular fSCC, illustrating a handful of cases, and noting that some well differentiated lesions were morphologically indistinguishable from keratoacanthoma (KA).[14] Kossard et al proposed that recognising a follicular pathway for cutaneous SCC, distinct from epidermal surface tumours, might be important biologically and that these tumours may be amenable to different therapeutic strategies.[14] In 2011 Misago et al published a small cases series ($n = 8$) of infundibular fSCC, including some large crateriform and KA-like lesions, with one case metastasising to local lymph nodes.[15] In 2013 Shendrik et al published the largest series of follicular SCC to date ($n = 61$) but comprising only 1.2% of all cutaneous SCC. Approximately half the cases showed clear cell cytology of ground-glass type that the authors considered consistent with tricholemmal differentiation and no case behaved aggressively at follow-up.[16]

In contrast to previous authors, that stated fSCC (infundibular and or pilar/tricholemmal) carcinoma to be rare (<2% of cutaneous SCC),[8,9,13,15,16] we propose that this subtype is massively under-recognised and common in every day sign-out. The follicular origin of many if not most SCC has major implications for diagnosis, staging, management and future research.[17,18]

Clinical features of follicular SCC

Follicular SCC arise on the hair bearing skin predominantly in those with significant sun-damage (80% head and neck), of the elderly (mean 75 years) with a male predominance (70%).[2,3,6–8,13,16,17]

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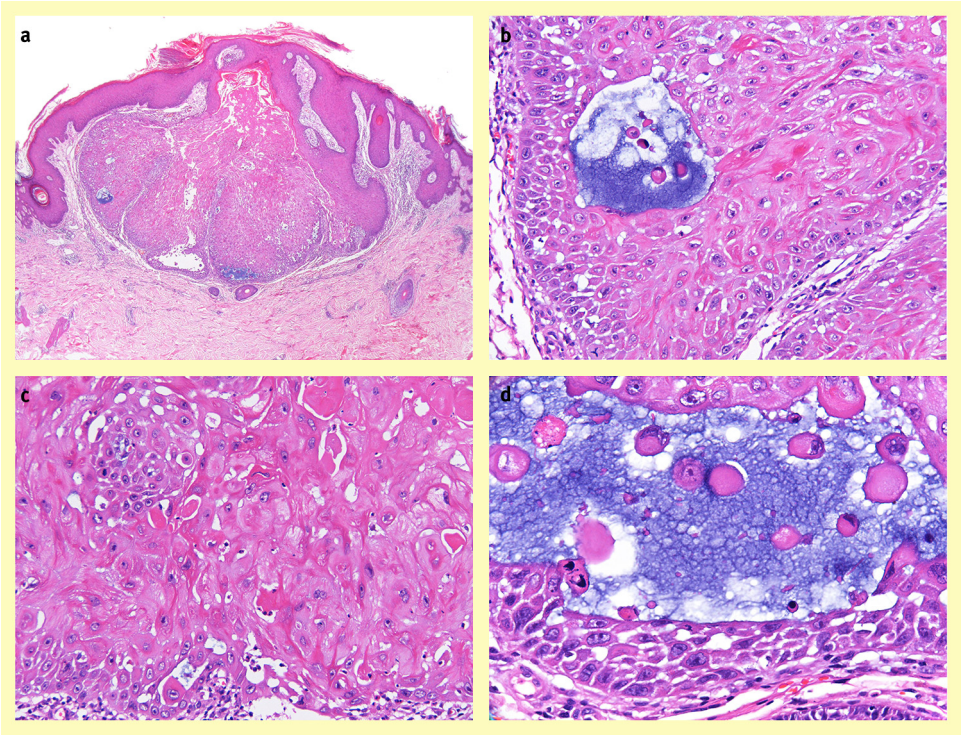

Figure 1 Follicular SCC, small in situ lesion. (**a**) Abrupt connection to surface at follicular infundibula. No background epidermal dysplasia. Rounded, entirely circumscript, borders. (**b**) Subtle palisading of peripheral cells. Central acantholytic mucin pool. (**c**) Distinctive abundant eosinophilic cytoplasm with individual cell abrupt (tricholemmal) keratinisation. (**d**) Acantholytic mucin pool. Mild to moderate pleomorphism.

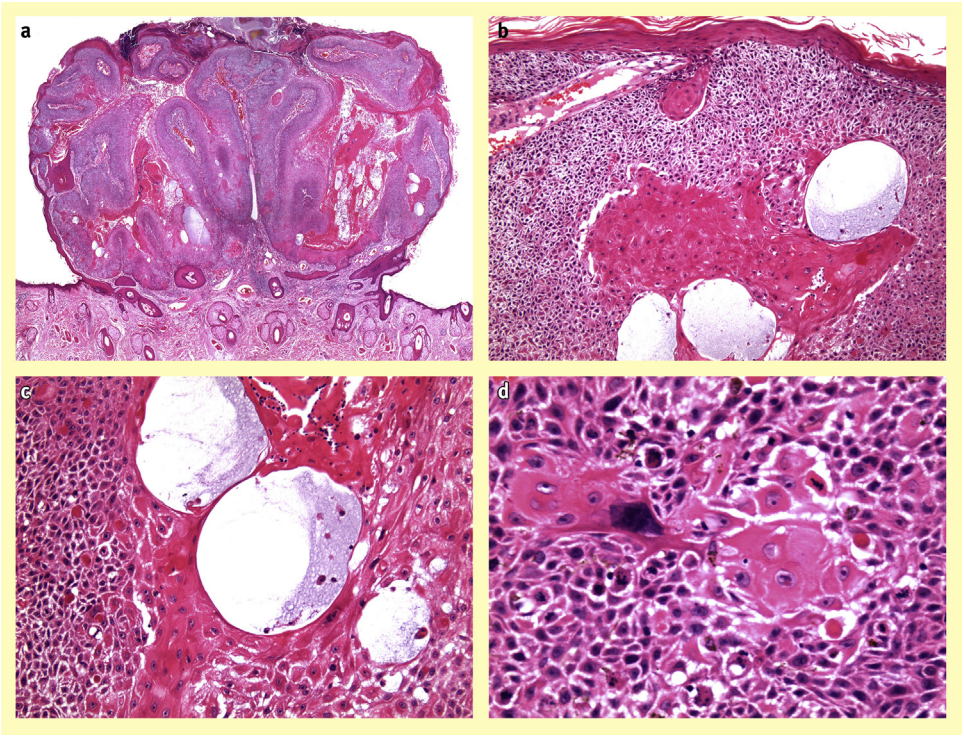

Figure 2 Follicular SCC, large exophytic in situ lesion. (**a**) Abrupt connections with epidermis that lacks dysplasia best appreciated peripherally. Confluent infundibular canals centrally obscure and replace the epidermis. Rounded, entirely circumscript borders. (**b**) Abrupt connection with epidermis that lacks dysplasia. (**b** and **c**) Prominent spongiosis of pale cells imparts a clear cell appearance. Central acantholytic mucin pools surrounded by distinctive tricholemmal cells with abundant orange-red cytoplasm. (**d**) Focal moderate to severe pleomorphism.