I present histologic documentation of a unique basal cell carcinoma (BCC) in which shadow cells formed the major cellular component along with extensive acantholysis and the development of ringed shadow cells. This neoplasm contained trichohyalin granules, which are indisputable evidence of follicular differentiation. Shadow cells rarely are encountered within BCCs and generally form relatively small components. Such neoplasms have been labeled BCC with matrical differentiation. Because of nonspecificity and ambiguity, I propose that this terminology be abandoned and replaced by shadow cell BCC.

Shadow cells rarely are encountered within basal cell carcinomas (BCCs). When present, shadow cells comprise relatively small portions of the neoplasm. Such neoplasms have been labeled BCC with matrical differentiation. My purpose is to report a unique case of a BCC in which not only did shadow cells form the major cellular component but also were associated with striking acantholysis. I therefore propose a different terminology for this form of BCC.

Case Report
A 64-year-old Caucasian man presented with an ulcerated circular papule involving the right temple. It measured 0.8 cm in diameter and had been present for almost one year. A 4-mm punch biopsy was performed, followed by an excisional biopsy 2 months later.

Histologically, the lesion proved to be a rare form of BCC. The lesion was deeply invasive and extended to involve approximately the upper half of the subcutaneous tissue. Shadow cells formed the major cellular component. Focally, this neoplasm was connected to both the epidermis and infundibula in association with suprabasilar clefts containing dyskeratotic acantholytic cells.

Clear spaces that ranged from small circular zones to clefts of variable length were randomly scattered throughout the neoplasm. A relatively small number of these spaces, primarily linear, did not possess an epithelial cell lining and undoubtedly represented stromal retraction artifact. The majority of spaces were either completely or partially lined by a single layer of palisaded basaloid cells (Figure 1). The small circular zones appeared adenoid or glandular. Many of these spaces contained clusters of acantholytic and focally dyskeratotic basaloid cells and rounded shadow cells (Figure 2). The cytoplasms of many of these shadow cells were filled with concentric laminations of keratin. Basaloid cells with crescent-shaped nuclei were attached to and either partially or totally encircled by many of the shadow cells that I labeled ringed shadow cells (Figure 3).

There was a broad range of histologic patterns within the neoplasm. At one end of the spectrum was the characteristic pattern of stromal proliferation with retraction artifact and peripheral palisading of basaloid cells with an orderly gradual progression of shadow cell formation. The sequence was as follows: a proliferation of several layers of basaloid cells with varying amounts of amphophilic to faintly eosinophilic cytoplasms that were focally vacuolated, the formation of transitional cells (cells with degenerating and necrotic nuclei), the transition into shadow cells, and the termination into compactly laminated keratin with focal calcification. In other areas, the transition into shadow cells was relatively abrupt, with little or no basaloid cell proliferation or transitional cells (Figure 4). At the other end of the spectrum, the neoplastic cells showed severe anaplasia. This was characterized by disorderly dyskeratotic cells with focally vacuolated cytoplasm, pleomorphic hyperchromatic nuclei, and frequent mitoses. Acantholysis also was present in these zones. This was evident by either partially coherent or slightly separated neoplastic cells

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associated with an intermingling of rounded or ringed shadow cells (Figure 5).

Trichohyalin granules, refractile granules that assume various sizes and shapes and stain brightly eosinophilic with hematoxylin and eosin (H&E), were identified within the cytoplasms of many basaloid cells (Figure 6). Brown melanin granules, which appeared black with the Fontana-Masson stain, were observed within dendritic melanocytes, basaloid cells, melanophages, and shadow cells in many areas (Figure 7). No mucin could be demonstrated within the neoplastic cells. Relatively large amounts of hyaluronic acid were observed within the stroma with special stains.

**Comment**

BCC of the skin is the most common primary invasive cancer of the human body. It may assume a variety of histologic patterns including solid, cystic, adenoid, sclerosing, keratotic (with horn cysts), and creeping. It may show either no evidence of differentiation or differentiation toward any or all of the cutaneous appendages. The basaloid cell is the diagnostic hallmark of this neoplasm and often may contain mucin, melanin, and lipid within its cytoplasm. Commonly, the basaloid cell shows squamous differentiation and becomes keratinized. Frequently, mucin, amyloid, and melanin within melanophages and dendritic melanocytes are observed within its stroma. Rarely, shadow cells form relatively small components of BCCs.4 Trichohyalin granules5 have also been identified within these BCCs.

Using the routine H&E stain, the typical shadow cell is recognized as a fully keratinized polyhedral cell with an abundant eosinophilic cytoplasm, a generally well-defined cytoplasmic border, and a central circular or oval empty space corresponding to the lost nucleus. When found within the skin, the shadow cell has been considered to represent a faulty attempt at the formation of a hair shaft and is indicative of follicular differentiation. Besides being a characteristic hallmark of the pilomatrixoma, shadow cells have been identified within a variety of pathologic processes involving the
epithelium of all 3 embryologically derived fundamental tissues—ectoderm, mesoderm, and endoderm. In addition to BCC and pilomatrixoma, ectodermally derived cutaneous lesions include alopecia areata; trichoepithelioma; mixed tumor of the skin; pilomatrix carcinoma, even within metastases; epidermal cysts of Gardner’s syndrome; proliferating pilomatrixoma; matricoma; melanocytic matricoma; condyloma acuminatum; and onychomycosis. Extracutaneous ectodermally derived shadow cells have been observed within a calcifying odontogenic cyst, an intracranial dermoid cyst, and a pilomatrixoma of the testis. With 2 exceptions, the shadow cells within the aforementioned lesions probably represent faulty attempts at follicular differentiation. Shadow cells within onychomycosis probably represent a faulty attempt to form the nail plate. Shadow cells within
the calcifying odontogenic cyst probably represent a final product of cell death from squamous metaplasia derived from enamel epithelium.

Entodermally derived lesions include adenocarcinoma of the colon with squamous differentiation; rectal adenocarcinoma, including lymph node metastasis; transitional cell carcinoma of the urinary bladder; and small cell carcinoma of the gallbladder. Mesodermally derived lesions include endometrial adenocarcinoma with squamous cell differentiation and atypical endometrial hyperplasia with squamous differentiation. In these lesions, the shadow cells, as noted within the calcifying odontogenic cyst, probably developed from squamous metaplasia.

It recently has been shown that the shadow cells in pilomatrixomas are a mode of cell death that

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develop from terminal differentiation of transitional cells, and represent an attempt to form hair (i.e., follicular differentiation). It is believed, however, that their formation is not necessarily specific for terminal differentiation into hair. This has been well documented within the nonsquamous, extracutaneous neoplasms previously described. In my view, this lesion must be differentiated from 3 neoplasms that appear histologically aggressive: adenoid (acantholytic, pseudoglandular) squamous cell carcinoma, proliferating pilomatrixoma, and pilomatrix carcinoma. The adenoid squamous cell carcinoma and this lesion share the features of ectodermally derived keratinocytes, continuity with the epidermis, suprabasilar clefts containing dyskeratotic acantholytic cells, and an invasive neoplasm with pseudoglandular formations containing dyskeratotic acantholytic cells. The major differences are the presence of shadow cells and, in this case, 

**Figure 6.** Large, deeply eosinophilic trichohyalin granules (arrow) within the cytoplasms of a few basaloid cells and acantholytic changes similar to those described in Figure 5 (H&E, original magnification ×400).

**Figure 7.** Coarse black melanin granules within a large dendritic melanocyte (center) and a melanophage (lower left) (arrow). Fine, dustlike, black melanin granules are present within virtually all of the basaloid cells and shadow cells depicted (Fontana-Masson stain, original magnification ×400).

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trichohyalin granules, which do not appear in squamous cell carcinomas of any type. Additionally, the clefts and pseudoglandular formations in this case are lined by basaloid cells, not dyskeratotic squamous cells, as are observed within the adenoid squamous cell carcinoma. Also, many of the acantholytic cells are shadow cells, often ringed by basaloid cells (ringed shadow cells). The significant features suggestive of squamous cell carcinoma are observed within the zones showing severe anaplasia. Although uncommon, it is not rare to find similar areas within BCCs. Proliferating pilomatrixoma and pilomatrix carcinoma are deep-seated nodules of variable size involving dermis and subcutaneous tissue. The former is generally well circumscribed, while the latter is poorly delineated and often invades subcutaneous fat and skeletal muscle. Both lesions contain cystic zones of variable size filled with keratinous debris along with a stromal foreign body reaction to keratin, calcium, and calcified shadow cells. Both lesions primarily are composed of peripheral aggregations of basaloid cells that merge, either abruptly or gradually via transitional cells, with shadow cells. The basaloid cells in proliferating pilomatrixoma resemble normal hair matrix cells. These basaloid cells are small rounded cells with scanty, pale eosinophilic cytoplasmics and circular nuclei with finely stippled chromatin and distinct nucleoli. Mitoses may be numerous. There may be variable nuclear atypia. Scattered necrotic basaloid cells are frequently observed. Although ulceration may be present, these basaloid cells do not communicate with the epidermis or infundibula. By way of contrast, the basaloid cells of pilomatrix carcinoma range from those resembling normal hair matrix cells to severely anaplastic cells with large hyperchromatic and pleomorphic nuclei and frequent mitoses, many abnormal, with varying amounts of cytoplasm. Foci of necrosis are common and often extensive. Ulceration is not unusual. Pilomatrix carcinoma may show connections to the epidermis but not to infundibula. Trichohyalin granules have been identified within the basaloid cells of both lesions.

Histologically, this case differs fundamentally from these 2 neoplasms. This is due to the absence of basaloid cells resembling normal hair matrix cells, the presence of peripheral palisading of basaloid cells with stromal retraction artifact, the presence of acantholysis, the absence of cystic zones, the absence of a foreign body reaction, and the presence of connections to both the epidermis and infundibula. The presence of melanin in this case lends further support for the diagnosis of BCC. It is a frequent component of BCCs. Although melanin-containing variants of many neoplasms of the pilar apparatus have been reported, they are uncommon. Additionally, the vacuolated cytoplasms observed within the basaloid cells in this case probably are indicative of lipid content, a commonly encountered component of BCCs.

The pilar apparatus is a complex miniature organ comprising hair follicle, sebaceous gland, apocrine gland, arrector muscle, and haarscheibe (hair disk). The pilar apparatus comes into existence embryologically through a continuous interaction between ectodermal and mesodermal components. The hair follicle is the most conspicuous part. Trichohyalin, a substance related to keratohyalin, occurs normally within the cytoplasms of the keratinizing cells of the inner root sheath and hair medulla. With the H&E stain, trichohyalin appears as bright, homogeneous, deeply eosinophilic, refractile structures of variable size and shape, ranging from fine granules to large rounded or irregular bodies. Melanocytes are ectodermal cells derived from the neural crest and are normal components of the matrix of a pigmented hair. Melanin is produced within these melanocytes and incorporated through phagocytosis of distal portions of dendritic processes into the future hair cells. The final product, the hair shaft, is composed primarily of hard keratin (cortex) without nuclei and with varying amounts of melanin. Melanin, keratin, and lipid are normal components of the pilar apparatus. Besides melanin and keratin, lipid deposits also probably were present in this case. None of these components is proof of follicular differentiation. The presence of trichohyalin, however, is specific and represents incontrovertible evidence of pilar differentiation.

Acantholysis means a pathologic loss of cohesion among keratinocytes of stratified squamous epithelia that is discernible with light microscopy. Although this term originally was restricted to lesions involving epidermis, follicular epithelium, and oral mucosa, adenoid squamous cell carcinoma has been included. It most often develops within an acantholytic actinic keratosis. In acantholysis, there is a breakdown of the forces of cohesion, which are intercellular substance and intercellular-attachment devices or desmosomes. It may be primary, such as occurs in pemphigus vulgaris, whereby the intracellular morphology appears normal under light microscopy. It also may be secondary, such as what occurs in adenoid squamous cell carcinoma and in this case, whereby acantholysis develops because of dyskeratotic changes.

In pemphigus vulgaris, electron microscopy has demonstrated that the tonofilaments within the acantholytic cells retract from the cell periphery...
and exhibit perinuclear aggregation. The spaces resulting from the loss of cohesion become filled with an influx of tissue fluid from the dermis. The acantholytic cells, occurring singly and in clusters, become rounded (actually spherical) within this fluid. I believe that this shape is a result of a combination of factors. These include loss of cohesion, uniform total surface tension (hydrostatic pressure) whereby the cells assume the smallest possible surface, and cell resilience, which is aided by an alteration in internal architecture.

Cell death is inevitable and may occur normally or abnormally. It normally is seen in the continuous shedding of soft keratin from the epidermis and the formation of hard keratin of nails and hair (all dead keratinized cells without nuclei). Within the various lesions previously discussed, shadow cells appear to represent an abnormal mode of cell death through faulty keratinization and, depending on their locale, may be indicative of hair or nail-plate differentiation or represent a mode of cell death from squamous metaplasia. BCCs containing shadow cells have been labeled BCC with matrical differentiation. I believe that this terminology is nonspecific and ambiguous. Although not specifically stated, this term is presumed to refer to the hair matrix. The skin, however, has other matrices. There are nail matrix cells, epidermal matrix cells, and adnexal matrix cells, which include those of the hair matrix. Furthermore, the meaning is unclear. Does the term indicate that the neoplastic cells are differentiating to form a hair shaft or that they are forming hair matrix cells? The latter certainly is not the case in these neoplasms. In my opinion, one simply should call this neoplasm as shadow cell BCCs with the understanding that the shadow cells are indicative of follicular differentiation.

In summary, I have presented a unique case of a BCC in which shadow cells formed the major cellular component. Not previously reported to my knowledge, this case also exhibited extensive acantholysis associated with a striking pattern of ringed shadow cells. This neoplasm contained trichohyalin granules that represent incontrovertible evidence of follicular differentiation. For the purpose of specificity and clarity, I propose that BCCs containing shadow cells be labeled shadow cell BCC.

REFERENCES


