Basaloid follicular hamartoma

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Basaloid follicular hamartoma is a benign lesion of important consideration because it can be mistaken both clinically and histologically for basal cell carcinoma. The formation of basaloid follicular hamartoma has been linked to a mutation in the patched gene, which is part of the same pathway implicated in nevoid basal cell carcinoma syndrome. While these hamartomas are considered benign lesions, malignant growths have been reported to arise within them, which raises the question, “Is basaloid follicular hamartoma a premalignant lesion?” Correct identification allows for periodic monitoring for malignant transformation, while sparing patients unnecessary surgery. Treatment strategies, including experimental therapies, are reviewed.

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Basaloid follicular hamartoma (BFH) is a rare, benign, superficial malformation of hair follicles that presents histologically as an epithelial proliferation of basaloid cells and clinically in various forms, with and without associated diseases.

This entity was first described in 1969 by Brown et al. as multiple papules in the nasolabial folds associated with myasthenia gravis and diffuse alopecia (Brown-Crounse syndrome). In 1985, the term basaloid follicular hamartoma was coined by Mehregan and Baker, who reported a localized and solitary type of lesion without associated abnormalities. Recently, Morohashi et al. described BFH as an abortive growth of secondary hair germs with a limited differentiation toward the upper follicular portion.

PATHOGENESIS

Genetic studies have linked BFH to a mutation in the patched (PTCH) gene on chromosome band 9q23. The gene is part of the same pathway implicated in nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin-Goltz syndrome, though its expression is less severe. The PTCH gene encodes a receptor for the protein product of the sonic hedgehog gene (SHH), a member of the hedgehog family of genes that are involved in developmental patterning during embryonic development. The PTCH receptor forms a receptor complex with another transmembrane protein known as SMO (for “smoothened”). When SHH protein is absent, PTCH receptor inactivates SMO and keeps it from transducing a downstream signal. Binding of SHH protein to the PTCH receptor releases the suppression of SMO, causing the upregulation of hedgehog target genes through a signal cascade that involves transcription factors in the Gli family. Unregulated signaling can lead to increased cell division resulting in abnormal growth and abnormal patterning.

Mutations in this pathway have been implicated in numerous abnormalities including NBCCS, sporadic basal cell carcinomas, trichoblastomas, trichoepitheliomas (TEs), cylindromas, nevus sebaceous, and dentigous cysts. Increased Gli-1 transcriptional activity, suggested as an underlying mechanism in BFH, is mitigated by treatment with retinoids, which decrease Gli-1 transcriptional activity. Studies are needed to further delineate the current understanding of BFH development.

CLINICAL FEATURES

Basaloid follicular hamartoma has varying clinical presentations and associations and may be localized or generalized. Basaloid follicular hamartoma may present as individual or linearly arranged, small, skin-colored to brown papules or plaques, or as multiple lesions in a generalized distribution on the face, scalp, and occasionally, the trunk. Basaloid follicular hamartoma may be a familial, congenital, or acquired condition. It may occur alone or in association with other genodermatoses and diseases, including Bazex-Dupre-Christol syndrome (an X-linked dominant disease characterized by early onset of multiple basal cell carcinomas, congenital hypotrichosis, and follicular atrophoderma), and has been reported in association with myasthenia gravis, alopecia, systemic lupus erythematosus, and cystic fibrosis.

The clinical differential diagnosis for BFH is dependent on the presentation. Individual papules may be misdiagnosed as basal cell carcinoma (BCC), intradermal melanocytic nevus, seborrheic keratosis, sebaceous hyperplasia, syringoma, angiofibroma, trichilemmoma, steatocystoma, TE, and hamartoma of sebaceous follicles.

Plaques may present like the lesions of nevus sebaceous, lupus erythematosus, and sarcoidosis. Basaloid follicular hamartoma in a linear distribution may mimic linear epidermal nevus, lichen striatus, linear morphea, and basal cell nevus.

Generalized BFH may represent generalized follicular hamartoma syndrome (Brown-Crounse syndrome), tuberous sclerosis, Cowden syndrome (“multiple hamartoma syndrome”) involving organs from all 3 germinal layers, multiple trichoepitheliomas, NBCCS, Rombo syndrome...
(atrophoderma vermiculatum of the face, multiple milia, telangiectases, acral erythema, and a propensity to develop BCC), and multiple tumors of the follicular infundibulum.4

GROSS FEATURES

Because of the varied clinical presentations of BFH, histologic specimens may be received in multiple forms including punch biopsies, shaves, or frozen sections of skin, without definite identifying gross features to distinguish BFH from other common skin lesions.

HISTOPATHOLOGY

Histologic examination narrows the differential diagnosis to lesions of epithelial basaloid proliferations and includes BFH, BCC, TE, and folliculocentric basaloid proliferation (FBP).

One of the most important considerations is whether the entity is benign or malignant. Finding follicular bulbs, papillary mesenchymal bodies, trichohyalin granules, hair shafts, shadow cells, and focal CD34 staining in adjacent tumor stromal cells all favor benign entities.5 Specifically, BFH consists of malformed and distorted hair follicles composed of cords and strands of basaloid cells. These cells are arranged in a radial and anastomosing fashion (Figure 1, A and B) and may arise from follicles and/or show an epidermal attachment.12 The tumor cells are bland without nuclear pleomorphism, and mitotic activity is rare or absent. There is scant to no single cell necrosis.4 While the presence of peripheral palisading has been reported,1,13 this feature is typically lacking in the degree seen in BCC.14,15 Stroma is scant or absent, and when present, consists of eosinophilic compact collagen with no fibrocytes. Clefts within the fibrous stroma have been reported.14,15 Minimal clefting between the tumor and stroma has been observed but is not a well-accepted feature of BFH.12 Usually, mucinous ground substance, if present, is subtle. Whether follicular bulbs and papillae are seen is debatable.14,16 Basaloid follicular hamartomas are seen only where normal follicles should be present. Therefore, they do not involve the interfollicular dermis nor do they involve the deeper reticular dermis.16

In contrast, BCC displays a variety of histologic patterns but is recognized as cords and islands of variably basophilic cells with hyperchromatic nuclei, embedded in a mucinous matrix, often surrounded by many fibroblasts and lymphocytes (Figure 1, A and C). Palisading of the cells at the periphery of the tumor islands is present. Clefts (separation artifact) are created as the stroma shrinks away from the epithelial tumor nests. Increased mitoses and single cell necrosis are also present. The neoplastic cells may involve and destroy preexisting hair follicles and interfollicular dermis and sometimes infiltrate deeper dermis, subcutaneous fat, and skeletal muscle.8,16

In 1987, Tozawa and Ackerman17 described a variant of basal cell carcinoma with follicular differentiation, named infundibulocystic basal cell carcinoma (ICBCC) (Figure 1, D). Since the histopathologic features of BFH are similar to those of ICBCC, some feel BFH and ICBCC represent a spectrum of the same entity.18 The premalignant potential of BFH is currently undetermined, although BCC arising within BFH has been reported.19 Requena et al18 described histopathologic and clinical criteria distinguishing BFH from ICBCC that include more prevalent malignant features in ICBCC, such as necrotic neoplastic cells, mitotic figures, and local tissue destruction.

A benign lesion in the differential diagnosis of BFH is TE (Figure 1, E). This neoplasm is composed of epithelium that differentiates toward hair structures. Histologically, TE has distinct islands of basaloid cells in a lacelike or adenoid network and, occasionally, as solid aggregates. They exhibit a more nodular growth pattern than BFH. The tumor islands show peripheral palisading like BCC. However, the stroma lacks the retraction artifact seen in BCC. In TE, the fibrocytic stroma is more prominent than in BFH and it predominates over the epithelial portion. In TE, normal follicular bulbs and papillae are seen.4,14,16 While both BFH and TE have keratin cysts consisting of a fully keratinized center surrounded by basophilic cells without high-grade atypia and mitoses, they are more prominent in TE.

Finally, FBP is a reactive lesion originating from mantle epithelium that occurs in clinically normal skin adjacent to a BCC (Figure 1, F). This is also known as “bulge” growth and may surround BCC for at least 3 mm.19,20 The major histologic features of FBP include folliculocentric, vertically oriented neoplasm with prominent hyaline basement membrane at the periphery of most basaloid aggregates and an unaltered stroma. Follicular papillae are absent or underdeveloped, although the lesion originates from the follicular outer root sheath. Histologically, BFH and FBP can at times be indistinguishable.20 The most notable difference between BFH and FBP is presence or absence of keratin cysts. No keratin cysts are reported in FBP,20 whereas keratin cysts are seen in BFH, TE, and ICBCC.19 No direct epidermal attachment is reported for FBP. Clear epidermal attachments are present in ICBCC and may be present in BFH.12,19,20

ANCILLARY STUDIES

Most of the basaloid epithelial proliferations can be identified histologically. Of the above differential diagnosis, differentiating BFH from BCC can be the most problematic. In these cases, special stains may help to delineate the lesion.

Ki-67 (a proliferative marker associated with mitosis) and Bcl-2 staining are more prominent in BCC than BFH (Figure 2, A through D). Bcl-2 stains only the outermost basal cells in BCC. CD34 is positive in stromal cells next to tumor cells in BFH and is negative in BCC (Figure 2, E and F). CD10 stains the peritumoral stroma of BFH as well as matrical cells, while BCC of various subtypes have stromal and tumor cell positivity.9,21 (Figure 2, G and H). Other stains reported to be useful for differentiation include PCNA (a subunit DNA polymerase that shows the proliferative fraction of tumor cells), which shows more prominent staining in BCC than in BFH. Also, PTCH mRNA is diffusely overexpressed in BCC, but it is overexpressed in BFH, only in cells having direct contact with the dermis. Finally, monoclonal anti-desmoglein antibody shows decreased staining in BCC, as malignant cells lose desmosomes.7,19

PROGNOSIS AND TREATMENT

Currently, there are no standard treatments for BFH. Correctly identifying BFH spares patients from unnecessary surgery, while allowing for periodic monitoring to detect malignant transformations or malignant growths within a BFH. Lesions with an increase in size or change of appearance should be biopsied. If associated with an
autoimmune disease, treatment of the autoimmunity may cause regression of the associated cutaneous lesions.

Some experimental therapies have been reported. In a report of cases,\textsuperscript{22} 5-aminolevulinic acid photodynamic therapy was found to be a safe, well-tolerated, and effective treatment for extensive areas of diffuse BCC and BFH, and it appeared to be the treatment of choice in children. Oral and topical retinoids caused regression of cutaneous BFH in another report.\textsuperscript{7} This therapy was effective because retinoids decrease Gli-1 transcriptional

Figure 1. A, A biopsy specimen with both basal cell carcinoma (left) and basaloid follicular hamartoma (right) suggests similar pathogenetic mechanisms. B, Basaloid follicular hamartoma shows vertically oriented basaloid cells arranged around a distorted hair follicle. Inset, Clefts within the fibrous stroma may be observed. C, Basal cell carcinoma forms islands of basophilic cells with peripheral palisading and artifactual clefting of stroma from tumor. D, Infundibulocystic basal cell carcinoma shows cords and nests of basophilic cells and keratin cysts with peripheral palisading of tumor cells. Inset, Prominent apoptosis is seen. E, Trichoepithelioma consists of basaloid tumor islands in a reticulated or interconnecting cord pattern with prominent keratin cysts and abundant loose stroma. F, Folliculocentric basaloid proliferation (FBP) shows basaloid aggregates of vertically oriented, folliculocentric neoplastic cells with unaltered stroma. Inset, The peripherally located hyaline basement membrane of FBP is prominent (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B, C, D, E, and F], ×400 [B, inset; D, inset; and F, inset]).
activity. A recent study found a hitherto unknown requirement for ligand-driven, canonical Wnt/β-catenin signaling for hedgehog pathway–driven tumorigenesis and has thus identified a new possible pharmacologic target for BFH. With additional studies, as a better understanding of BFH is obtained, pharmacologic agents are promising future treatment possibilities.

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References

Figure 2. Special stains help to differentiate basaloid follicular hamartoma from basal cell carcinoma. A, Basaloid follicular hamartoma showing weak nuclear positivity for Ki-67. B, Basal cell carcinoma showing strong nuclear positivity for Ki-67. C, Basaloid follicular hamartoma demonstrating weak cytoplasmic positivity for Bcl-2 in the outermost tumor cells only. D, Basal cell carcinoma demonstrating more prominent cytoplasmic staining for Bcl-2. E, Basaloid follicular hamartoma showing CD34 positivity in stromal cells next to tumor cells. F, Basal cell carcinoma does not stain with CD34. G, Basaloid follicular hamartoma showing weak positivity for CD10 in peritumoral stromal cells. H, Basal cell carcinoma showing CD10 positivity in the cytoplasm of tumor cells (Ki-67, original magnifications ×400 [A and B]; Bcl-2, original magnifications ×400 [C and D]; CD34, original magnifications ×400 [E and F]; CD10, original magnifications ×400 [G and H]).