C A S E R E P O R T

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Solitary basaloid follicular hamartoma: a report of two cases and a brief review of the literature

Solitarni bazaloidni folikularni hamartom: prikaz dva bolesnika i kratak pregled literature

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Abstract

Introduction. Basaloid follicular hamartoma (BFH) is a rare benign follicular malformation often clinically misdiagnosed. Patients with BFH demonstrate a variety of clinical manifestations and associated abnormalities. BFH may be a familial, congenital, or acquired condition with a localized or generalized distribution. Several clinical variants of generalized BFH are recognized, which may be associated with a diverse spectrum of abnormalities. **Case report.** We present two cases of solitary BFH in pediatric patients. The first patient was a 16-year-old boy with a history of autism spectrum disorder, admitted to our department for consultation due to a harmless dermal nevus on his face. The second patient was a six-year-old girl presented with a ten-month history of an asymptomatic, skin-colored papule located on the right nasolabial fold that gradually increased in size over time. Both cases were documented dermoscopically, and they were presented with a brief overview of the current literature. **Conclusion.** Considering the overlapping clinical, histological, and dermoscopic features of BFH with other benign and malignant lesions, its incidence in pediatric patients is probably higher than what is reported in the current literature.

Key words:
dermoscopy; diagnosis; immunohisochemistry; hamartoma; histological techniques.

Apstrakt

Uvod. Bazaloidni folikularni hamartom (BFH) je retka benigna folikularna malformacija koja se često pogrešno dijagnostikuje. Bolesnici sa BFH ispoljavaju različite kliničke manifestacije i udružene abnormalnosti. BFH može biti familijarna, kongenitalna ili stečena malformacija, sa lokalizovanom ili generalizovanom distribucijom. Opisano je nekoliko kliničkih varijanti generalizovanih BFH, koje mogu biti udružene sa širokim spektrom abnormalnosti. **Prikaz bolesnika.** Prikazujemo dva slučaja solitarnog BFH kod pedijatrijskih bolesnika. Prvi bolesnik je 16-godišnji dečak sa istorijom poremećaja iz spektra autizma, koji je primljen na odeljenje na konsultaciju zbog bezopasnog nevusa na licu. Drugi bolesnik je šestogodišnja devojčica sa desetomesečnom istorijom asimptomatske papule boje kože na desnoj nazolabijalnoj brazdi, koja se vremenom uvećavala. Oba slučaja su dermoskopski dokumentovana i prikazana uz kratak pregled aktuelne literature. **Zaključak.** Imajući u vidu kliničku, patohistološku i dermoskopsku sličnost BFH sa drugim benignim i malignim lezijama, njegova incidenca u pedijatrijskoj populaciji je verovatno viša nego što je u aktuelnoj literaturi prikazano.

Ključne reči:
dermoskopija; dijagnoza; imunohistohemija; hamartom; histološke tehnike

Introduction

Basaloid follicular hamartoma (BFH) is a benign follicular malformation often clinically misdiagnosed. Although observed as a relatively rare hamartoma, BFH is probably underreported due to a variable clinical presentation that may lead to diagnostic difficulties. BFH may be a congenital, familial, or acquired condition. Several clinical variants of BFH have been described, including the localized (solitary and multiple lesions) and generalized

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forms, with the latter being mostly associated with systemic syndromes and various diseases such as myasthenia gravis, systemic lupus erythematosus (SLE), cystic fibrosis (CF), and alopecia [1–7]. Herein, we report two cases of solitary BFH in pediatric patients.

Case reports

Case 1

A 16-year-old boy with a history of autism spectrum disorder was admitted to our Department for consultation due to a harmless dermal nevus on his face. According to his mother, his past medical and family history was unremarkable. During the total body skin examination, a small, slightly pigmented papule was noticed on his lower back (Figure 1A). A dermoscopic examination of the lesion highlighted the presence of bluish-gray dots and globules over the brownish background with a linear irregular vessel (Figure 1B). The excisional biopsy was performed with a presumptive diagnosis of basal cell carcinoma (BCC). Standard histopathological (HP) methods [hematoxylin and eosin staining and immunohistochemical (ICH) analysis] were used for diagnostic purposes. Monoclonal mouse antibody against Bcl-2 (clone 124, DAKO, ready-to-use), CD34 (clone QBEnd 10, DAKO, ready-to-use), and CD10 (clone 56C6, DAKO, ready-to-use) were applied for ICH analysis after 4 μm thick, paraffin-embedded tissue selection was deparaffinized in xylene and rehydrated in graded ethanol series. In brief, tissue selections were treated with citrate buffer (pH 6.0) in a microwave oven for 20 min for antigen retrieval. After endogenous peroxidase activity block and rinsing with phosphate-buffered saline, each slide was incubated with primary antibody for one hour. Overall, an HP examination revealed numerous cords and strands of basaloid cells arranged in a radial and anastomosing pattern over the scant fibrous stroma (Figure 2A). Basaloid cells showed subtle peripheral palisading without nuclear pleomorphism, mitotic activity, and the presence of

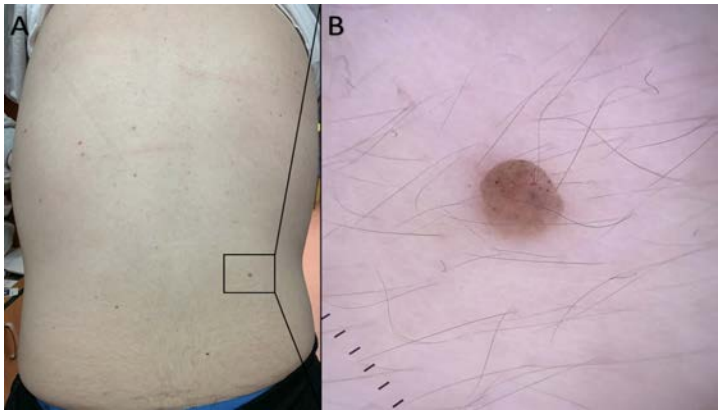

Fig. 1 – Case 1: clinical and dermoscopic features of basaloid follicular hamartoma in a boy: A) solitary papule on his right lumbar region; B) multiple blow globules and linear vessels observed on dermoscopy.

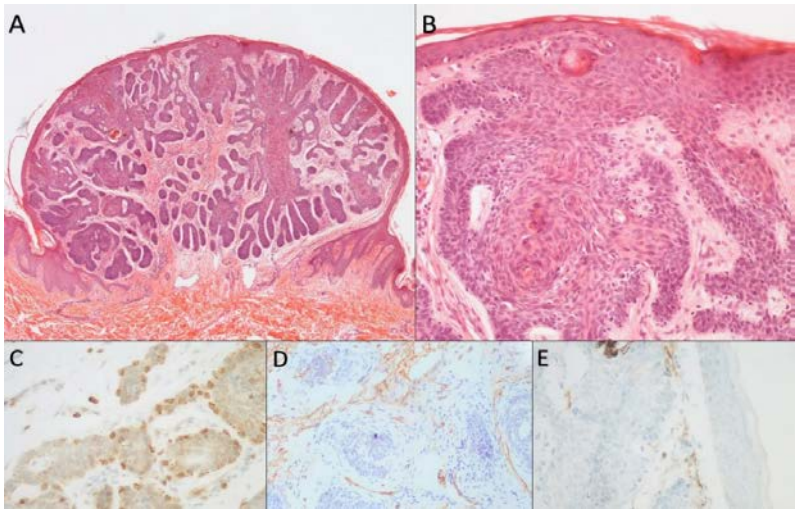

Fig. 2 – Case 2: histopathological and immunohistochemical (ICH) features of basaloid follicular hamartoma: A) cords and strands of basaloid cells arranged in a radial and anastomosing pattern [hematoxylin and eosin (HE) staining, ×4]; B) basaloid cells with subtle peripheral palisading without nuclear pleomorphism, mitotic activity, and the presence of cell necrosis (HE staining, ×10); C) Bcl-2 positivity in peripheral basaloid cells (ICH, ×20); D) CD34 positivity in stromal cells (ICH, ×20); E) CD10 positivity in stromal cells (ICH, ×20).

cell necrosis (Figure 2B). Additionally, ICH analysis revealed positivity of peripheral basaloid cells for Bcl-2 (Figure 2C), as well as CD34 and CD10 stromal cells positivity (Figure 2 D and E). Overall, those features were consistent with a diagnosis of BFH.

Case 2

A six-year-old girl presented with a ten-month history of an asymptomatic, skin-colored papule located on the right nasolabial fold (Figure 3A) that gradually increased in size over time. During a dermoscopy assessment, linear irregular vessels were noticed over the whitish-pinkish background (Figure 3B). Based on the clinical and dermoscopic features alone, suspicion of skin adnexal neoplasm was considered. An excisional biopsy was performed, and the HP examination revealed the presence of cords and strands of bland-looking basaloid cells with a branching and anastomosing pattern in the superficial dermis (Figure 4A). IHC staining for Bcl-2, CD34, and CD10 were obtained, showing Bcl-2 positivity in peripheral neoplastic cells (Figure 4B) and both positive staining for CD34 and CD10 in stromal cells (Figure 4 C and D) (method previously described). Considering HP and IHC features, a diagnosis of BFH was made.

Discussion

BFH, originally described in 1969 by Brown et al. [8] and later termed by Mehregan and Baker [9] in 1985, is a rarely encountered follicular malformation with diverse clinical presentations. According to genetic studies, the development of BFH involves a mutation in the patched homolog (PTCH) gene located on the chromosome band 9q23, a tumor suppressor gene also implicated in the pathogenesis of basal cell nevus syndrome (BCNS) [10, 11]. Namely, the PTCH gene product acts as a part of the receptor for the sonic hedgehog (SHH) protein, which has a fundamental role in numerous aspects during embryonic development. The PTCH protein forms a receptor

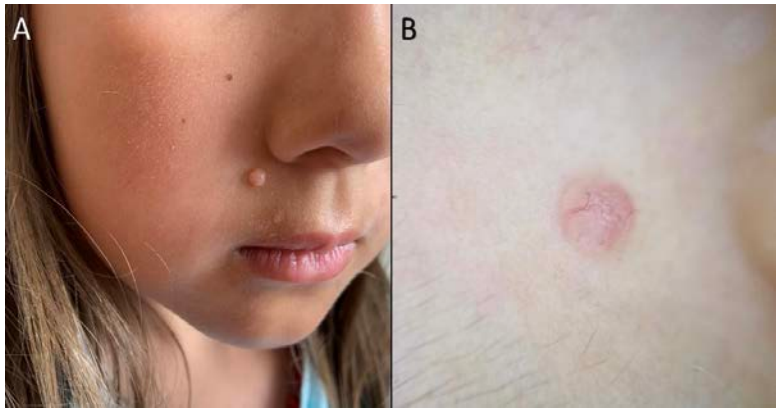

Fig. 3 – Clinical and dermoscopic features of basaloid follicular hamartoma in a girl: A) solitary non-pigmented papule on the right nasolabial fold; B) linear irregular vessels over the whitish-pinkish background observed on dermoscopy.

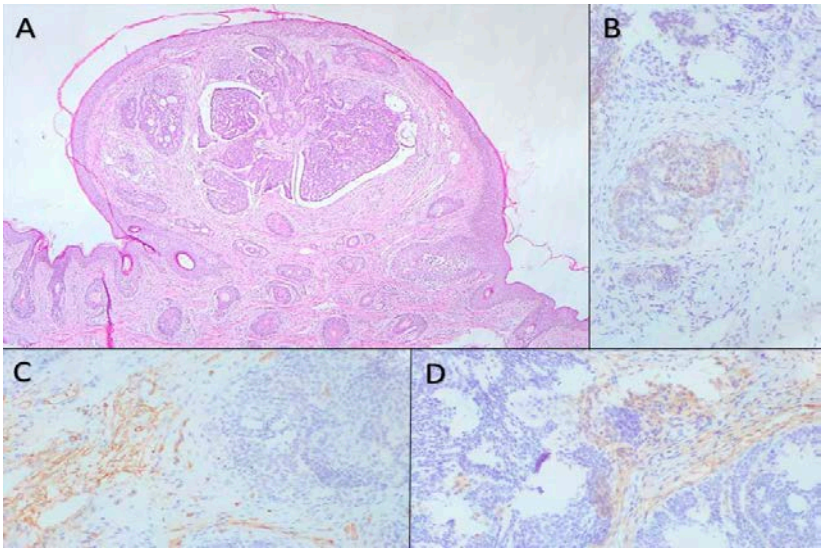

Fig. 4 – Histopathological and immunohistochemical (IHC) features of basaloid follicular hamartoma: A) cords and strands of basaloid cells arranged in a radial and anastomosing pattern with subtle peripheral clefting (hematoxylin and eosin staining, ×4); B) Bcl-2 positivity in peripheral basaloid cells (ICH, ×20); C) CD34 positivity in stromal cells (ICH, ×20), and D) CD10 positivity in stromal cells (ICH, ×20).

complex with a transmembrane signaling protein smoothened (SMO). In the absence of SHH protein, the PTCH receptor prevents the transduction of the downstream signal through the inactivation of SMO. In contrast, when SHH binds to the PTCH receptor, it releases the inhibition of SMO, which in turn leads to the upregulation of hedgehog target genes by transcription factors in the Gli family [10, 11]. Activation of this signaling pathway may lead to increased cell proliferation, resulting in abnormal growth and lesion formation [3, 10, 11].

Patients with BFH demonstrate a variety of clinical manifestations and associated abnormalities. BFH may be a familial, congenital, or acquired condition with localized or generalized distribution. In the context of localized disease, BFH may be present as a solitary lesion or display a linear and/or unilateral arrangement of multiple lesions [1–6]. Most described cases of localized BFH were situated on the scalp and face, although other locations, including the trunk and extremities, are also possible. Lesions usually clinically appear as a skin-colored to brown papule, plaque, or patches of alopecia in the case of scalp involvement [1–8]. Contrary to localized forms, generalized BFHs are commonly associated with a diverse spectrum of abnormalities. Several clinical variants of generalized BFH are recognized, including the following: a sporadic form of multiple BFHs without a systemic disease; an acquired form associated with alopecia and autoimmune diseases, including myasthenia gravis and SLE; a familial form with autosomal dominant inheritance with or without associated abnormalities, including multiple milia, comedo-like lesions, hypotrichosis, hypohidrosis, palmar and/or plantar pits (also known as generalized BFH syndrome); finally, a congenital form of multiple BFHs associated with alopecia and CF [3–7]. Additionally, BFH may occur in association with genodermatoses such as Bazex-Dupre-Christol syndrome, BCNS, and Happle-Tinschert syndrome (unilateral and segmental BFHs occurring along Blaschko's lines) [1–7].

Depending on the clinical presentation alone, a broad list of differential diagnoses should be considered. Dermal melanocytic nevi, BCC, trichoepithelioma, trichilemmoma, sebaceous hyperplasia, seborrheic keratosis, syringoma, acrochordons, and angiofibroma should be ruled out in case of solitary BFH. Linear BFH may be misdiagnosed as linear epidermal nevus, linear lichen striatus, and linear morphea, while generalized BFH may mimic BCNS, tuberous sclerosis, Cowden syndrome, Rombo syndrome, and multiple trichoepitheliomas [1, 11].

From HP aspects, BFH is composed of radial and anastomosing cords and strands of basaloid cells that display an epithelial attachment and/or arise from follicles. The basaloid cells are typified by bland morphology without pleomorphic nuclei, mitotic activity and cell necrosis. If the presence of peripheral palisading is observed, it should be focal and lacking in the degree typically seen within BCC. Beyond those observations, keratin cysts may be seen inside basaloid cords. Lesions of BFH are superficial and only appear where normal hair follicles are present. Therefore, interfollicular and deeper reticular dermis are not affected. The surrounding stroma is scant and consists of eosinophilic compact collagen and a small number of fibrocytes. While minimal retraction clefts between neoplastic tissue and stroma are occasionally reported in BFH, this feature is typical for BCC or trichoepithelioma. Regarding the IHC, BFH has a low proliferative rate, which can be demonstrated with Ki-67 expression in a small number of cells. Bcl-2 positivity may be observed in the outermost basaloid cells of BFH, while CD34 and CD10 are both expressed within stromal cells [11, 12].

Regarding HP, lesions that should be differentiated from BFH include BCC, trichoepithelioma, and folliculocentric basaloid proliferation. The differential diagnosis between BFH and BCC may be challenging, given the overlapping features of cords and stands of basaloid cells in both lesions. However, in BCC, basaloid cells reveal an increased mitotic activity, single-cell necrosis, as well as pronounced palisading and clefting. Furthermore, the neoplastic basaloid nests of BCC tend to involve the interfollicular dermis and destroy pre-existing hair follicles. BCC has been reported to display a higher Ki-67 mitotic index, prominent Bcl-2 staining, and a lack of expression of CD34 in stromal cells. Abundant stroma with numerous fibrocytes, prominent keratin cyst formation, and the presence of papillary mesenchymal bodies in trichoepithelioma allow a straightforward differentiation from BFH. A folliculocentric basaloid proliferation is a reactive proliferation of mantle epithelium that occurs in the skin adjacent to BCC. HP features that favor the diagnosis of folliculocentric basaloid proliferation over BFH include a vertically oriented basaloid proliferation with a surrounding prominent basement membrane and the absence of both keratin cysts and direct epidermal attachment [11, 12].

Although HP findings are consistent in all clinical variants of BFH, the dermoscopic appearance of this rare hamartoma is quite variable [13–18]. Namely, dermoscopic features of BFH are scarce and limited to a few case reports. Mauleón et al. [14] were the first ones to report a dermoscopy of BFH, which displayed an unspecific structureless blue pattern. Other reported dermoscopic features of BFH include a structureless brown pattern [15], a papillomatous and cobblestone pattern with brown-black globules, dots, and comedo-like openings, bluish-gray and brownish globules over the pinkish background with linear irregular vessels [13, 18]. Recently, Besagni et al. [18] published three pediatric patients of BCNS with multiple BCCs and BFHs, revealing dermoscopic features of bluish-gray globules and nests within both types of lesions and typical arborizing vessels in BCCs. They highlighted the vascular pattern as a possible dermoscopic clue when differentiating between those lesions [18]. However, in both of our cases, the vascular pattern was apparent and could now support that observation.

Conclusion

We reported two cases of solitary BFH in pediatric patients, whose incidence is probably higher than what is reflected in the current literature considering overlapping clinical, histological, and dermoscopic features of other benign and malignant lesions, particularly BCC. BFH should be considered in the differential diagnosis of solitary lesions in the pediatric population.

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