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Case Report Open Access

Multiple Basaloid Follicular Hamartomas in Blaschko`S Lines with and without Extracutaneous Malformations: Towards a Unifying Concept

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Abstract

Background: Basaloid follicular hamartomas (BFHs) may occur as single isolated tumors, as localized tumors or as multiple tumors in a disseminated or in a patterned distribution. Non-hereditary multiple and mostly unilateral basaloid follicular hamartomas arranged according to Blaschko`s lines with associated extracutaneous malformations have been designated as a genetic mosaicism disease and one entity. The transition of BFH into basal cell carcinoma as well as the formation of concurrent extracutaneous malignancies has been published.

Methods: We present a case of multiple and unilateral basaloid follicular hamartomas arranged according to Blaschko`s lines in multiple and anatomically separated skin areas but lacking extracutaneous malformations. Its clinical features are compared to published cases and discussed on the basis of recent findings in embryology.

Results: We would propose the hypothesis that in multiple and unilateral BFHs with or without extracutaneous symptoms, the affected cell clone arises shortly before or during gastrulation and comprises only a small fraction of cells of the epiblast. The mutated cells are then displaced and mixed with normal cells by a collective whorl-like migration of epiblast cells as it has been observed by life-microscopy in chicken embryogenesis. This could explain the predominantly unilateral distribution of BFHs in Blaschko`s lines as well as the dispersal of mutated cells along the anterior-posterior axis.

Conclusions: The proposed mechanism leading to multiple and mostly unilateral BFHs in Blaschko`s lines with or without extracutaneous symptoms might serve as a blueprint for other mosaicizm diseases with cutaneous symptoms and facultative extracutaneous malformations.

Keywords: Basaloid follicular hamartoma; Happle-Tinschert syndrome; Blaschko`s lines; Mosaicism; Epiblast

Abbrevations:

BFHs: Basaloid Follicular Hamartomas; BLs: Blaschko`s Lines

Background

The term basaloid follicular hamartoma (BFH) was first used in 1985 by Mehregan and Baker and describes a rare skin adnex tumor, putatively originating from abortive hair follicle formation [1]. The first case not yet named BFH was described in 1952 [2]. Basaloid follicular hamartomas (BFHs) may histologically be misdiagnosed as basal cell carcinoma or trichoepithelioma [3]. Immunohistochemistry helps to make the distinction and reveals a reduced proliferative potential of BFHs in comparison to basal cell carcinoma [4-6].

The malignant potential of BFHs, especially with respect to transition into basal cell carcinoma, remains unspecified [5,7] but case reports have described transition to basal cell carcinoma [1,2,8-10] as well as concurrent extracutaneous malignancies [11,12].

Basaloid follicular hamartomas may occur as single isolated tumors, as localized tumors or as multiple tumors in a disseminated or in a patterned distribution [13,14]. BFHs may be congenital or acquired later in life. Most isolated BFHs are single acquired tumors located on the face or scalp and are primarily detected in elderly patients [13,15]. BFHs are described as localized when aggregates of BFHs are found in a localized plaque, mainly on the head [1]. Localized BFHs may be congenital [15]. A hereditary autosomal dominant disease with congenital and generalized BFHs without extracutaneous malformations has been designated as generalized basaloid follicular hamartoma syndrome, MIM 605827 [16-18]. To our knowledge, there is only one case report describing hereditary BFHs in association with cystic fibrosis [19]. A distinct syndrome seems to be represented by multiple non-hereditary acquired BFHs in a non-patterned distribution and associated with autoimmune diseases [20-23]. Besides, BFHs may also be observed in lesionary skin of patients with nevoid basal cell carcinoma syndrome (NBCCS) and Bazex-Dupré-Christol syndrome [14,24].

All cases with multiple BFHs in a patterned skin distribution described hitherto were either diagnosed at birth or early in life and were not hereditary [14]. Moreover, it seems that most multiple BFHs in a patterned distribution only affect one side of the body [14,25] although bilateral involvement has been described [26]. Cases with patterned distribution were designated with different adjectives such as systematized [1], linear [2], zosteriform [27], nevoid [28] or

segmentally arranged [14]. Several authors clarify that the so named patterns follow Blaschko's lines [12,14,25,29]. It is assumed that Blaschko`s lines (BLs) reflect the migration patterns of epidermal cells and subsequent folding of the skin during embryogenesis [30]. Blaschko's lines become visible when an epidermal cell lineage displays altered growth characteristics as in epidermal nevus or induces altered pigmentation as in incontinentia pigmenti due to postzygotic somatic mosaicism or due to functional mosaicicsm resulting from alternant gene silencing [31].

Linear grouping of BFH may also be seen in some cases of hereditary generalized BFHs, but Happle and Tinschert pointed out that in these cases the linear distribution does not follow BLs [14]. Several patients with unilateral BFHs in a patterned distribution also demonstrated associated and mostly ipsilateral extracutaneous malformations [12,14,27,28]. Happle and Tinschert suggested that the combination of unilateral multiple BFHs distributed according to Blaschko`s lines associated with mostly ipsilateral osseous, dental and cerebral anomalies represents a distinct syndrome, most probably due to genetic mosaicism [14]. This syndrome was later named Happle-Tinschert syndrome [12].

The sonic hedgehog (SHH) signaling pathway has been implicated in the formation of BFHs. The SHH-signaling pathway is formed, among others, by gene products of sonic hedgehog (SHH), patched (PTCH1), smoothened (SMO) as well as GLI genes [32]. BFHs have been observed in patients with Gorlin-Golz-Syndrome [24] which harbours germline mutations in PTCH1 [33]. Moreover, it has been demonstrated that genetically modified mice with SMO or GLI2 mutations develop BFHs [34,35]. Defects in SSH-signalling have been demonstrated in polydactyly and teeth defects [36], features also found in Happle-Tinschert syndrome [14,37]. On the other hand, in humans mutations in PTCH1 or SMO have only been detected in basal cell carcinoma but not in BFHs [12,25,38]. It has been speculated that BFHs may develop when SHH-signaling is only moderately activated, while strong activation of SHH-signaling would lead to basal cell carcinoma [39,34].

This paper focuses on multiple unilateral basaloid follicular hamartomas in Blaschko`s lines distribution with or without associated extracutaneous malformations. The authors present an additional case and assume that clinical picture as well as facultative association of extracutaneous malformations can be explained sufficiently by postzygotic mosaicism and by putative migration patterns of epidermal cell precursors during gastrulation.

Methods

The clinical and histologic features of a patient with multiple and unilateral basaloid follicular hamartomas arranged according to Blaschko`s lines in multiple and anatomically separated skin areas but lacking extracutaneous malformations is presented. The patient consented to the publication.

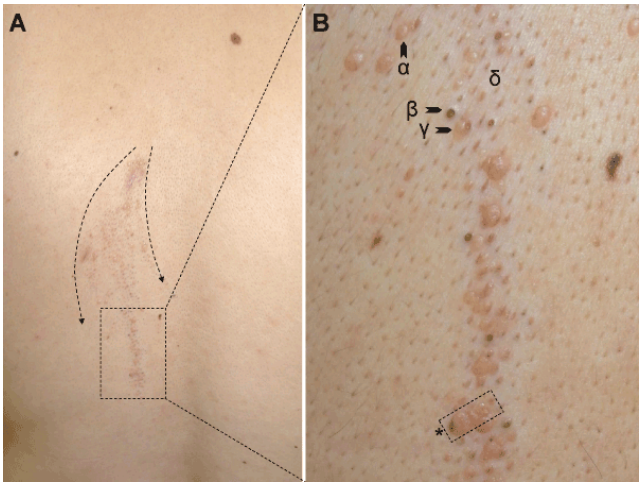

Figure 1: Patches of multiple BFHs on the lower back. A: Overview. Arrows: Putative direction of dispersal of mutated cells giving rise to BFHs. B: Details, Asterix: Biopsy area.

Case Report

A 42-year-old patient was admitted to our department with skin abnormalities following BLs. They had been present since early childhood. Anamnesis revealed a recent change in texture of skin lesions located on the back. Lesions appeared to be asymptomatic and the patient had not received any treatment prior to the current consultation. There was no family history on record neither for similar lesions nor for other skin diseases. The patient had no alopecia, dental anomalies, skeletal anomalies, neurologic symptoms or other pathological findings.

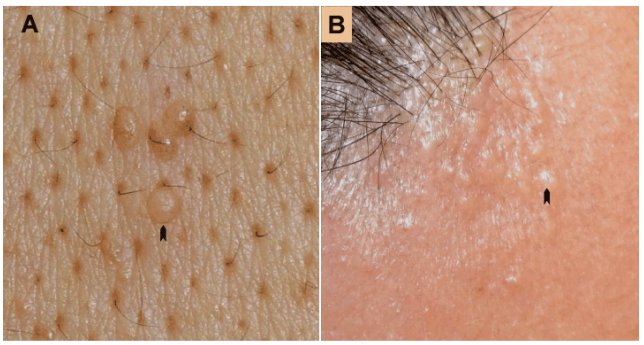

Figure 2: A: Small area with BFHs on the left shoulder. B: Lesions on the left side of the forehead.

On physical examination, four patches with multiple skin coloured or slightly yellowish papules and few comedo-like horn plugs were seen on the patients lower back (Figure 1), on the left shoulder (Figure 2A), on the ventral side of the neck and on the frontal part of the scalp extending to the forehead (Figure 2B). Lesions were exclusively located on the left body side and were grouped in vortex-like configurations following the lines of Blaschko. Marcroscopically, papules either substituted for a terminal hair follicle (Figure 1B, α) or were adjacent

to a normal terminal hair follicle (Figure 2A, arrow). Comedo-like horn plugs also substituted for a terminal hair (Figure 1B, β). Some comedo-like horn plugs were associated with papules (Figure 1B, γ). The interfollicular skin appeared lighter in areas with multiple grouped papules (Figure 1B, δ). It was further observed that site and spacing of the papules on the back reflected arrangement of normal terminal hair follicules (Figures 1B and 2A). On the forehead, papules were smaller and resembled miliae. Some seemed to be associated with vellus hair follicles (Figure 2B, arrow).

An excisional biopsy was taken from lesional skin on the back (Figure 1B, asterix). Histopathology demonstrated typical features of BFH (Figure 3). Small tumors beneath normal appearing epidermis consisting of multiple strands of basaloid cells arranged in a lattice-like pattern originated either from hair follicles or from sprouting hair germ-like structure in the proximity of existing hair follicles (Figure 3A, arrow, figure 3B, asterix). Some follicles were dilated and contained horn material. BFHs stained positive with Ber-EP4 (Figure 3B), a monoclonal antibody which reacts with tissues showing follicular germinative differentiation [38]. Proliferation marker cyclin D1 stained fewer cells within BFHs compared to suprabasal epithelial cells of epidermis and hair follicle (Figure 3C). No immunoreactivity was detected within BFHs when using an antibody against human androgen receptor (Figure 3D). Intense and uniform staining of BFHs was detected when using antibodies against p63 and CK 5/6 and no immunoreactivity was detected with antibodies against CK7 (not shown).

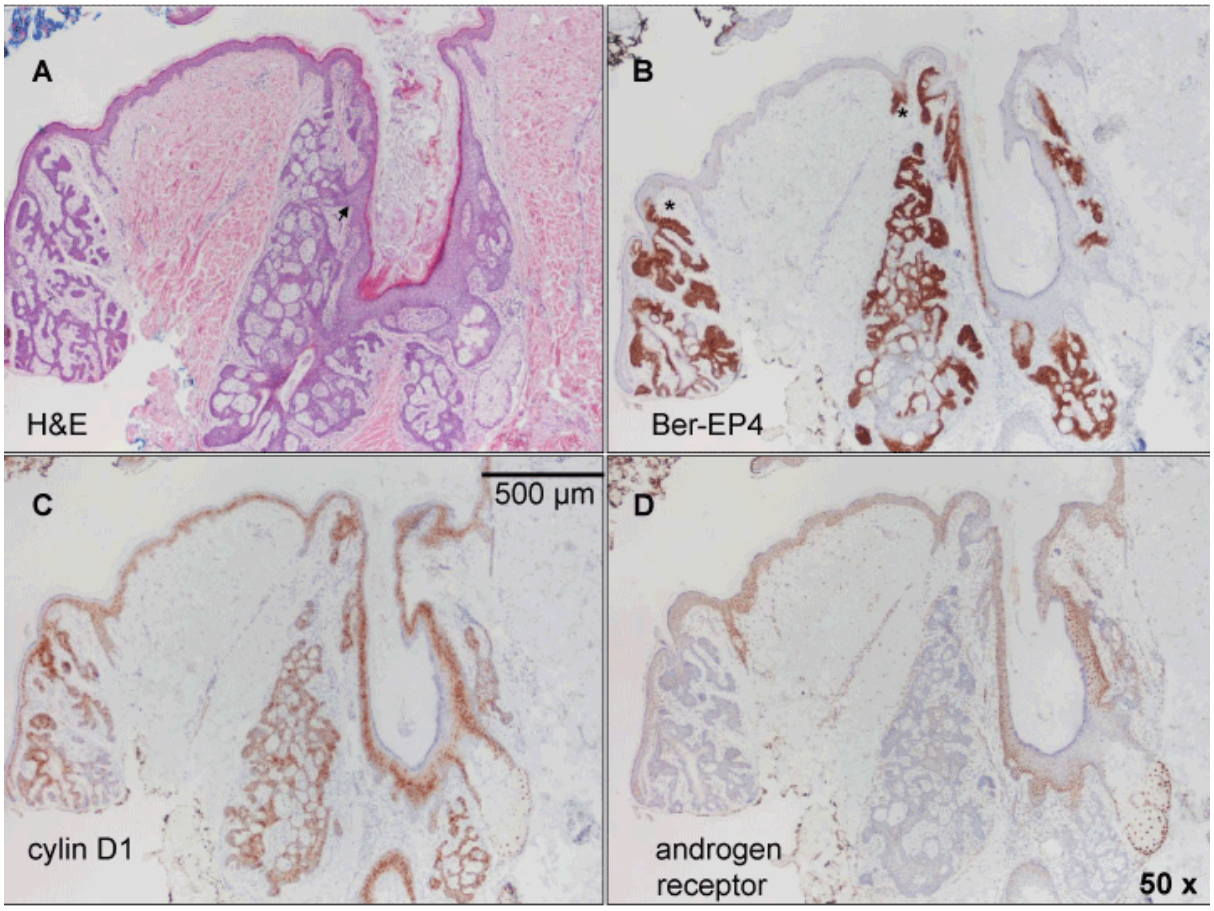

Figure 3: A-D: Histology and immunohistochemistry of the skin area with BFHs as indicated by figure 1B.

Discussion

The presented case demonstrates all cutaneous features of Happle-Tinschert syndrome but lacks its extracutaneous malformations. The challenge is to integrate the clinical picture of the case report as well as the published reports on multiple and mostly unilateral basaloid follicular hamartomas in Blaschko`s lines with and without extracutaneous malformations into a unifying pathological and developmental concept while the underlying genetic alteration has not been characterized yet.

Analysis of macroscopic details of BFHs in multiple and unilateral BFHs in BLs reveals some clues as to the formation of BFHs and the underlying molecular processes. It has been stated that BFHs result from abortive hair follicle formation [1,40,41]. It has also been noted that BFHs may not only originate from the hair follicles but also from epidermal strands sprouting from the interfollicular skin [41]. This has been observed in the presented case as well. As already described by Mehregan in 1985 [1], BFHs may be present adjacent to normal hair follicles or they may replace hair follicles or even form cyst like structures. In the analyzed case, BFHs further reflected localization and spacing of surrounding terminal hair follicles. We are tempted to

speculate that somatically mutated epithelial cells respond with dermal invasion and proliferation secondary to dermal signals inducing normal hair follicle development and maintenance. When mutated cells are restricted to interfollicular skin adjacent to a hair follicle, a BFH will develop adjacent to a normal hair follicle. When mutated cells comprise the hair follicle, they might either form cyst-like structures or form a BFH which replaces the hair follicle.

Multiple and mostly unilateral BFHs arranged according to Blaschko's lines and with associated extracutaneous anomalies must be considered a mosaicism disease [14]. The principal arguments for post-zygotic mosaicism are the arrangement of the lesions in BLs and the fact that this entity has never been observed as a hereditary disease. This further implies that the responsible mutation is autosomal and dominant as well as lethal in germline. A recessive mutation could have created defects arranged in BLs due to loss of heterozygosity occurring at an early embryological developmental stage [42] but then the disease would have been hereditary. The described extracutaneous symptoms of Happle-Tinschert syndrome include severe and mostly unilateral defects of brain and bones which emphasizes the assumption of embryonic lethality of the underlying mutation [14,43]. On the molecular scale, the assumed genetic alteration most probably represents a gain of function mutation or an activating mutation within a promoter region and it could be related to SHH-signaling.

It seems reasonable to assume that multiple and unilateral BFHs arranged according to BLs without associated extracutaneous anomalies might represent a milder expression of Happle-Tinschert syndrome where fewer mutated cells are present. The presence of fewer mutated cells in a mosaicism disease due to post-zygotic mutation implies a later occurrence of the mutation during embryogenesis.

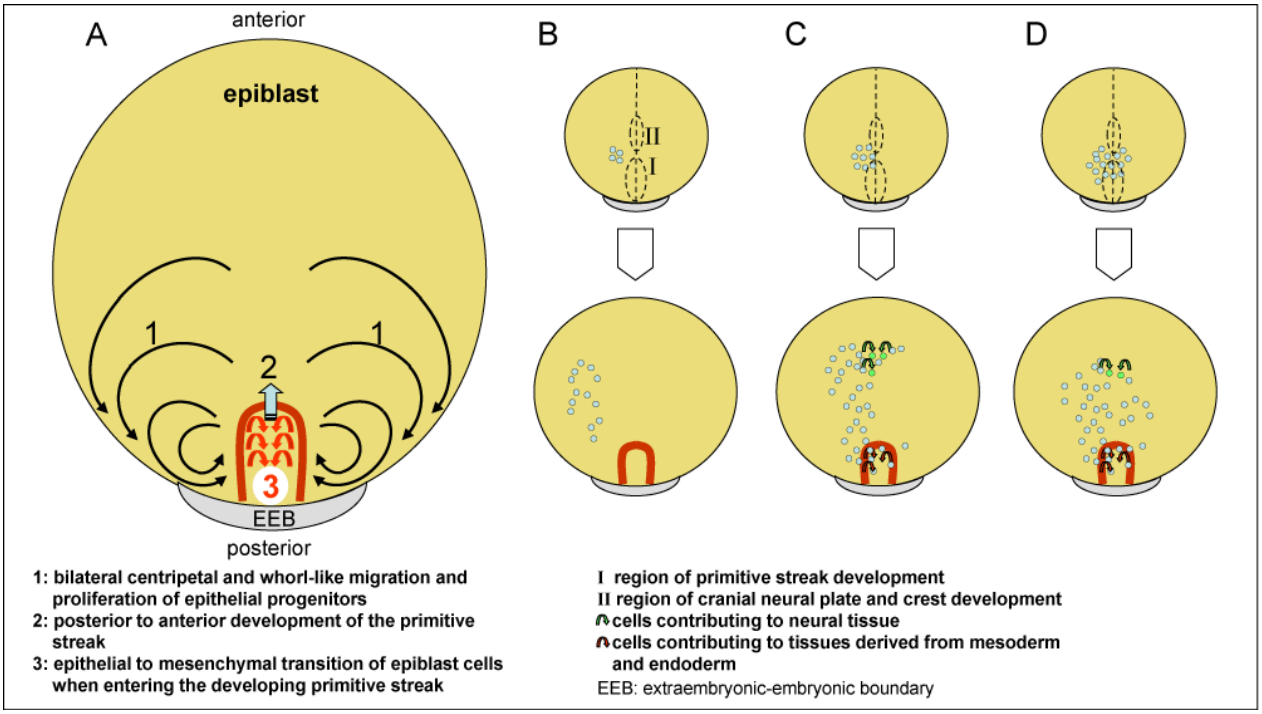

Figure 4: A: Putative collective epiblast cell movement during gastrulation according to Chuai et al. [43]. B: Schematic drawing of dispersal of mutated cells in multiple and unilateral BFHs in BLs without extracutaneous anomalies. C: Schematic drawing of dispersal of mutated cells in Happle-Tinschert syndrome with midline crossing of mutated cells. D: Schematic drawing of dispersal of mutated cells in Happle-Tinschert syndrome with mutated cells on both sides of the epiblast.

Nonetheless, we would like to propose a more elaborate scheme based on newer findings in vertebrate embryology [44-46]. Lateralization of the mammalian embryo becomes obvious with the formation of the primitive streak which defines the anterior-posterior axis and divides the epiblast in left and right (Figure 4A). Formation of the primitive streak also initiates gastrulation, i.e. the formation of the ectoderm, mesoderm and endoderm.

The case presented and Happle-Tinschert syndrome have in common that they not only display mostly unilateral BFHs but also show BFHs in multiple and anatomically separated skin areas. In addition, BFHs do not cover whole unilateral segments of skin but only very limited patches surrounded by normal skin. This seems to be characteristic of many published cases of multiple and unilateral BFHs in BLs [2,8,12,14,27,28]. It implies that the mutation responsible for BFH formation must arise in only a small subset of epidermal precursor cells, which have not terminated their migration or displacement along the anterior-posterior axis of the epiblast. Only migration or displacement of already mutated cells along the anterior-posterior axis combined with mixing of these mutated cells with normal cells might explain the presence of multiple and separated unilateral patches of BFHs which encompass multiple body segments.

This assumption fits well with recent findings in chicken embryogenesis where in-vivo visualization of cell migration during gastrulation demonstrated that cells of the epiblast migrate collectively

in whorls on each side of the developing primitive streak [44,45]. This vortex migration of epiblast cells displaces and mixes cells along the anterior-posterior axis as well as laterally (Figure 4A). Epiblast cells later form the ectoderm and skin epithelium but they also contribute to the mesoderm and endoderm as cells located near the posterior midline enter the primitive streak and undergo epithelial to mesenchymal transition. Moreover, cells near the anterior midline later contribute to the neural plate and crest.

We therefore propose the hypothesis that in multiple and unilateral BFHs, the affected cell clone arise shortly before or during gastrulation and comprise only a small fraction of cells of the epiblast. In multiple BFHs without extracutaneous symptoms, these putative mutated cells might be located in a region of the epiblast which does not provide cells undergoing epithelial to mesenchymal transition at the primitive streak and which does not contribute significantly to the neural plate or neural crest (Figure 4B). Extracutaneous defects could arise when mutated cells undergo epithelial to mesenchymal transition at the primitive streak or when mutated cells contribute to the neural plate or neural crest (Figure 4C).

In Happle-Tinschert syndrome, BFHs as well as extracutaneous symptoms may occasionally be detected on both body sides although in most cases one body side is affected more severely [14]. Two mechanisms which do not exclude each other could explain both, the occurrence of bilateral skin lesions as well as bilateral extracutaneous defects. One could assume that the putative whorl-like migration of epiblast cells during gastrulation allows for a limited transition of cells to the contralateral side. This assumption is backed by the observation that Blaschkos`s lines on the trunk sometimes cross the dorsal midline. The mutated cells could pass the dorsal midline where epithelial to mesenchymal transition at the primitive streak takes place and thereby induce bilateral extracutaneous defects. (Figure 4C). Bilateral defects would also arise when the mutation occurs prior to gastrulation in a region of the embryo which contributes cells to both sides of the epiblast (Figure 4D).

Hypotheses on putative mechanisms which govern the distribution of mutated cells in a mosaic human body are important as they shed light on human embryologic development which cannot be studied using experimental setups. Nevertheless, it has to be stressed that the proposed hypotheses on the role of collective epiblast cell migration in explaining symptoms in Happle-Tinschert syndrome and Blaschko's line formation are only derived from live microscopy findings in chicken embryogenesis. Collective epiblast cell migration during gastrulation still awaits confirmation in mammalian and human embryogenesis. Further insights into cell dynamics during embryogenesis as well as elucidation of the mutations responsible for BFHs will be necessary to definitely classify the different clinical conditions which are characterized by basaloid follicular hamartomas.

Author's Contributions

ML treated the patient and carried out the literature review and drafted the manuscript. TB performed the histologic studies. AR conceived the concept. All authors read and approved the final manuscript.

References

1. Mehregan AH, Baker S (1985) Basaloid follicular hamartoma: three cases with localized and systematized unilateral lesions. J Cutan Pathol 12: 55-65.
2. Carney RG (1952) Linear unilateral basal-cell nevus with comedones; report of a case. AMA Arch Derm Syphilol 65: 471-476.
3. Huang SH, Hsiao TF, Lee CC (2012) Basaloid follicular hamartoma: a case report and review of the literature. Kaohsiung J Med Sci 28: 57-60.
4. Naeyaert JM, Pauwels C, Geerts ML, Verplancke P (2001) CD-34 and Ki-67 staining patterns of basaloid follicular hamartoma are different from those in fibroepithelioma of Pinkus and other variants of basal cell carcinoma. J Cutan Pathol 28: 538-541.
5. Stashower ME, Smith K, Corbett D, Skelton HG (2001) Basaloid/follicular hyperplasia overlying connective tissue/mesenchymal hamartomas simulating basal cell carcinomas. J Am Acad Dermatol 45: 886-891.
6. Ramos-Ceballos FI, Pashaei S, Kincannon JM, Morgan MB, Smoller BR, (2008) Bcl-2, CD34 and CD10 expression in basaloid follicular hamartoma, vellus hair hamartoma and neurofollicular hamartoma demonstrate full follicular differentiation. J Cutan Pathol 35: 477-483.
7. Mills O, Thomas LB (2010) Basaloid follicular hamartoma. Arch Pathol Lab Med 134: 1215-1219.
8. Jiménez-Acosta FJ, Redondo E, Baez O, Hernandez B (1992) Linear unilateral basaloid follicular hamartoma. J Am Acad Dermatol 27: 316-319.
9. Yoshida Y, Urabe K, Mashino T, Duan H, Kiryu H, et al. (2003) Basal cell carcinomas in association with basaloid follicular hamartoma. Dermatology 207: 57-60.
10. Pujol RM, Nadal C, Matias-Guiu X, PeyrÃ J, FerrÃ¡ndiz C, et al. (1998) Multiple follicular hamartomas with sweat gland and sebaceous differentiation, vermiculate atrophoderma, milia, hypotrichosis, and late development of multiple basal cell carcinomas. J Am Acad Dermatol 39: 853-857.
11. Ricks M, Elston DM, Sartori CR (2002) Multiple basaloid follicular hamartomas associated with acrochordons, seborrhoeic keratoses and chondrosarcoma. Br J Dermatol 146: 1068-1070.
12. Itin PH (2009) Happle-Tinschert syndrome. Segmentally arranged basaloid follicular hamartomas, linear atrophoderma with hypo- and hyperpigmentation, enamel defects, ipsilateral hypertrichosis, and skeletal and cerebral anomalies. Dermatology: 221-225.
13. Brownstein MH (1992) Basaloid follicular hamartoma: solitary and multiple types. J Am Acad Dermatol 27: 237-240.
14. Happle R, Tinschert S (2008) Segmentally arranged basaloid follicular hamartomas with osseous, dental and cerebral anomalies: a distinct syndrome. Acta Derm Venereol 88: 382-387.
15. Yang XC, Yan H, Hao F, Yie QY, Zhong BY (2010) Congenital localized basaloid follicular hamartoma: a case report and review of the literature. Int J Dermatol 49: 443-447.
16. Wheeler CE, Carroll MA, Groben PA, Briggaman RA, Prose NS, et al. (2000) Autosomal dominantly inherited generalized basaloid follicular hamartoma syndrome: report of a new disease in a North Carolina family. J Am Acad Dermatol: 189-206.
17. Patel AB, Harting MS, Smith-Zagone MJ, Hsu S (2008) Familial basaloid follicular hamartoma: a report of one family. Dermatol Online J 14: 14.
18. Girardi M, Federman GL, McNiff JM (1999) Familial multiple basaloid follicular hamartomas: A report of two affected sisters. Pediatr Dermatol 16: 281-284.
19. Mascaró JM Jr, Ferrando J, Bombí JA, Lambruschini N, Mascaró JM (1995) Congenital generalized follicular hamartoma associated with alopecia and cystic fibrosis in three siblings. Arch Dermatol 131: 454-458.
20. Brown AC, Crounse RG, Winkelmann RK (1969) Generalized hair-follicle hamartoma, associated with alopecia, aminoacidura, and myasthenia gravis. Arch Dermatol 99: 478-493.
21. Ridley CM, Smith N (1981) Generalized hair follicle hamartoma associated with alopecia and myasthenia gravis: report of a second case. Clin Exp Dermatol 6: 283-289.
22. Morton S, Stevens A, Powell RJ (1998) Basaloid follicular hamartoma, total body hair loss and SLE. Lupus 7: 207-209.

23. Smith KJ, Skelton H (2003) Basaloid follicular hamartomas associated with autoimmune disease: a possible role for retinoids in therapy. J Am Acad Dermatol 49: 1067-1070.
24. Gartmann H, Groth W, Quinkler C (1989) [Multiple basaloid follicular hamartomas in 2 members of a family with Gorlin-Goltz syndrome]. Z Hautkr 64: 915-918.
25. Yébenes M, Toll A, Vélez M, Barranco C, Alonso-López NA, et al. (2008) Linear unilateral hamartomatous basal cell naevus with glandular and follicular differentiation. Clin Exp Dermatol 33: 429-432.
26. Waxweiler WT, Adigun CG, Groben P, Rubenstein DS (2011) A novel phenotype with features of basal cell nevus syndrome and basaloid follicular hamartoma syndrome. J Am Acad Dermatol 65: e17-19.
27. Liao KD, Chuan MT, Yu HR, Peng Y (1999)Basaloid follicular hamartoma. Dermatol Sinica : 165-171.
28. El-Darouti MA, Marzouk SA, Abdel-Halim MR, Zidan AZ, Fawzy MM (2005) Basaloid follicular hamartoma. Int J Dermatol 44: 361-365.
29. Lee MW, Choi JH, Moon KC, Koh JK (2005) Linear basaloid follicular hamartoma on the Blaschko's line of the face. Clin Exp Dermatol 30: 30-34.
30. Happle R (2002) Dohi Memorial Lecture. New aspects of cutaneous mosaicism. J Dermatol 29: 681-692.
31. Molho-Pessach V, Schaffer JV (2011) Blaschko lines and other patterns of cutaneous mosaicism. Clin Dermatol 29: 205-225.
32. Li C, Chi S, Xie J (2011) Hedgehog signaling in skin cancers. Cell Signal 23: 1235-1243.
33. Hahn H, Christiansen J, Wicking C, Zaphiropoulos PG, Chidambaram A, et al. (1996) A mammalian patched homolog is expressed in target tissues of sonic hedgehog and maps to a region associated with developmental abnormalities. J Biol Chem 271: 12125-12128.
34. Grachtchouk V, Grachtchouk M, Lowe L, Johnson T, Wei L, et al. (2003) The magnitude of hedgehog signaling activity defines skin tumor phenotype. EMBO J 22: 2741-2751.
35. Grachtchouk M, Pero J, Yang SH, Ermilov AN, Michael LE, et al. (2011) Basal cell carcinomas in mice arise from hair follicle stem cells and multiple epithelial progenitor populations. J Clin Invest 121: 1768-1781.
36. Ming JE, Roessler E, Muenke M (1998) Human developmental disorders and the Sonic hedgehog pathway. Mol Med Today 4: 343-349.
37. Kim J, Zambrano EV, McNiff JM (2007) Congenital panfollicular nevus associated with polydactyly. J Cutan Pathol 34 Suppl 1: 14-17.
38. Brailey LL, Davis T, Kolker SE, Murry TC, Thomas D, et al. (2007) Congenital linear unilateral basal cell nevus: a case report with patched gene molecular studies. J Cutan Pathol 34: 65-70.
39. Ansai S, Takayama R, Kimura T, Kawana S (2012) Ber-EP4 is a useful marker for follicular germinative cell differentiation of cutaneous epithelial neoplasms. J Dermatol 39: 688-692.
40. Kato N, Ueno H, Nakamura J (1992) Localized basaloid follicular hamartoma. J Dermatol 19: 614-617.
41. Morohashi M, Sakamoto F, Takenouchi T, Hashimoto T, Tago O, et al. (2000) A case of localized follicular hamartoma: an ultrastructural and immunohistochemical study. J Cutan Pathol 27: 191-198.
42. Poblete-Gutierrez P, Wiederholt T, Konig A, Jugert FK, Marquardt Y, et al. (2004) Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest: 1467-1474.
43. Boccaletti V, Accorsi P, Pinelli L, Ungari M, Giordano L, et al. (2011) Congenital systematized basaloid follicular hamartoma with microphthalmia and hemimegalencephaly. Pediatr Dermatol 28: 555-560.
44. Cui C, Yang X, Chuai M, Glazier JA, Weijer CJ (2005) Analysis of tissue flow patterns during primitive streak formation in the chick embryo. Dev Biol 284: 37-47.
45. Chuai M, Hughes D, Weijer CJ (2012) Collective epithelial and mesenchymal cell migration during gastrulation. Curr Genomics 13: 267-277.
46. Nowotschin S, Hadjantonakis AK (2010) Cellular dynamics in the early mouse embryo: from axis formation to gastrulation. Curr Opin Genet Dev 20: 420-427.

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