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 mosaicism diseases with cutaneous symptoms and facultative extracutaneous malformations.

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

Abbreviations:
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 mosaicism 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), smoohened (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. Macroscopically, 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 follicles (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).

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.

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

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 with 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.
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 anterior-posterior axis and the 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).

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**


This article was originally published in a special issue, entitled: “Skin Cancer”, Edited by Dr. Homer S. Black, Baylor College of Medicine, USA