

CLINICAL REPORT

Segmentally Arranged Basaloid Follicular Hamartomas with Osseous, Dental and Cerebral Anomalies: A Distinct Syndrome

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A 39-year-old man presented with multiple basaloid follicular hamartomas involving the right side of his body in a systematized pattern following Blaschko's lines. His right leg was 22.5 cm shorter than the left, and rudimentary pre-axial polydactyly was noted on the left hand and the right foot. The teeth of the right maxilla were hypoplastic. DNA analysis of blood lymphocytes and fibroblasts from lesional skin did not reveal any mutation in the Patched gene. On account of this case and of 8 similar cases found in the literature, the spectrum of a distinct syndrome is delineated. Ipsilateral extracutaneous defects include cervical ribs, polydactyly, malformed thumb and disproportionate overgrowth or deficient growth of limb bones; dental anomalies in the form of anodontia, hypodontia or ameloblastoma; and cerebral defects such as mental retardation, unsteady gait, meningioma and optic glioma. The cutaneous lesions of this syndrome should not be called "basal cell naevus" as this will lead to continuing confusion with Gorlin syndrome. The molecular basis of the disorder remains to be elucidated. Key words: basaloid follicular hamartoma; bone defects; brain lesions; dental anomalies; mosaicism; segmental involvement.

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Basaloid follicular hamartoma (BFH) is a rare benign tumour of the hair follicle with characteristic histopathological features (1, 2). This adnexal tumour, which is often misdiagnosed as trichoepithelioma or basal cell carcinoma, may occur as a solitary lesion (2), as multiple disseminated BFH with an autosomal dominant mode of transmission (3, 4), as non-familial linear BFH (5, 6) or, possibly, as a syndrome characterized by disseminated BFH associated with alopecia and myasthenia gravis (2).

The aim of this paper is to delineate a distinct syndrome characterized by a segmental manifestation of densely arranged BFH associated with ipsilateral osseous, dental and cerebral abnormalities. We present here a patient affected with this disorder and 8 pertinent case

reports published previously under various designations in dermatological journals.

CASE REPORT

A 39-year-old man presented with unilateral skin lesions and osseous anomalies noted since birth. His parents were healthy and non-consanguineous. He had a younger brother who was also healthy. His right leg was 22.5 cm shorter than the left, and he had reduced mobility in the right hip joint. Premature closure of epiphyses of the right femur and tibia was noted on X-rays at the age of 13 years. In early childhood macroglossia was noted and surgical correction of this problem was performed at the age of 5 years. Since then his tongue had been deviating to the right side.

On physical examination, a saddle nose and hypoplastic teeth of the right maxilla without visible defects of the enamel or dentin were noted. The skin of his hands and feet appeared to be rather loose. Rudimentary pre-axial polydactyly was present on the left hand and the right foot. Several linear areas covered with multiple skin-coloured or yellowish or brownish papules that, in part, showed central horn plugs resembling comedones, involved the trunk and the limbs on the right side (Fig. 1). They formed S-figures on the trunk, a whorl on the lower part of the abdomen, and a perpendicular pattern on the limbs, thus following Blaschko's lines. The right side of the chest was hairless (Fig. 2), and on the abdomen the band-like regions were somewhat atrophic. Moreover, linear areas of atrophoderma and hyperpigmentation involved the right arm and were most conspicuous on the hand (Fig. 3). Similar atrophic and hyperpigmented lesions were noted on the right lower leg. In addition, a linear area of hypertrichosis was present on the dorsal aspect of the right foot, and numerous atypical plantar pits were noted on this side (Fig. 4). On the left side, two scar-like whitish plaques were present on the ulnar surface of the fifth finger, whereas the sole showed two small atypical pits.

The patient's gait was somewhat unsteady and this appeared to be independent of his limp resulting from body asymmetry and problems with the right hip joint.

Histopathological examination of a papule revealed typical features of BFH. From the infundibular area of

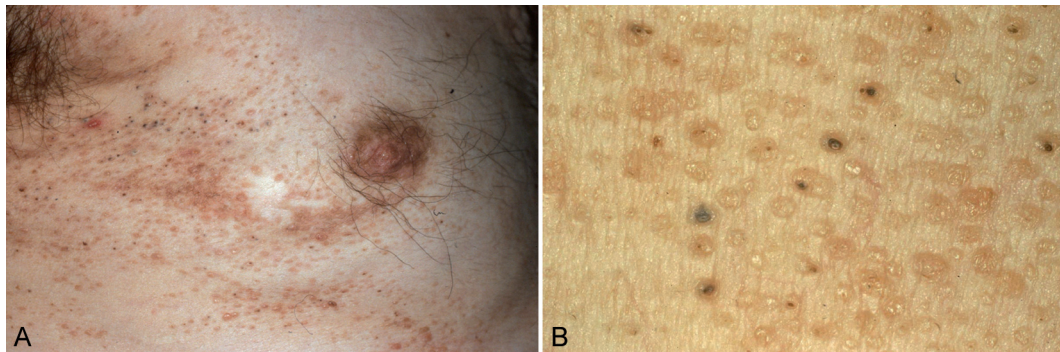


Fig. 1. Segmentally arranged basaloid follicular hamartomas (A) involving the right side of the chest and (B) showing in part comedo-like plugging.

a hair follicle, multiple strands of squamoid or basaloid cells proliferated and formed numerous anastomoses giving rise to a lattice-like pattern (Fig. 5A). The surrounding stroma was rather scarce. In addition, multiple horn cysts were noted (Fig. 5B).

Chromosome analysis of peripheral blood lymphocytes and fibroblasts derived from the affected skin showed a normal male karyotype 46,XY. A search for mutations in the Patched gene (*PTCH*) was performed as published previously (7) by sequencing the protein-coding region of genomic DNA that was isolated from peripheral blood lymphocytes, and from cultured fibroblasts derived from an involved skin area. No mutation was detected in the *PTCH* coding region.

DISCUSSION

The cutaneous and extracutaneous anomalies present in this patient, when compared with several similar cases reported in the literature under various designations, appear to represent a distinct phenotype. The existence of this entity, however, has so far not been established in textbooks of dermatology or medical genetics (8–11). Therefore, the characteristic features of this syndrome are delineated below.

Cutaneous anomalies

A clinical hallmark of this multisystem birth defect is the presence of segmentally and rather densely arranged skin-coloured or brownish papules. In the newborn, the cutaneous lesions have been described as “whitish, glistening and elevated” (12). Histopathological examination shows strands of squamoid or basaloid cells that proliferate downwards from the follicular infundibulum, forming horn cysts and numerous anastomoses resulting in a lattice-like pattern, whereas the stroma is rather scant (1, 2). In part, the papules have a central comedo-like plug (13), which is why “comedones” in association with linear BFH have been reported by several authors (14, 15) and have even given rise to an erroneous diagnosis of “naevus comedonicus syndrome” (16). The segment involved by BFH may be hypopigmented or hyperpigmented (12), and it may show areas of atrophoderma (15, 17, 18) as was seen in the present case. In our patient, patches of either hairlessness or hypertrichosis were noted. A “generalized hypertrichosis” reported by Burck et al. (19) may be caused by anticonvulsive therapy, although a strikingly asymmetric involvement, as shown on a photograph, suggests a primary nosological relationship to the syndrome. Moreover, palmar or plantar atypical pitting has been reported (12, 16) and was also found in the present case.



Fig. 2. Ipsilateral hypotrichosis with strict midline separation.



Fig. 3. Right hand showing linear atrophoderma with pronounced hyperpigmentation.



Fig. 4. Right sole showing linear atrophoderma and atypical pits.

Contralaterally, small patches of multiple BFH or other skin lesions were documented by Burck et al. (19) and in the present case.

Rarely noted cutaneous findings include loose skin of hands and feet (as in the present case) and dystrophic toenails (18). The patient reported by Burck & Held (12) had "a cutaneous hump in the midline of her nose bridge". Aloi et al. (18) noted plaques of cutaneous and subcutaneous ossification within the involved segments of the body.

Skeletal anomalies

The bone abnormalities are usually localized ipsilaterally and comprise cervical rib (20), pre-axial or postaxial polydactyly including rudimentary forms (16, 21), and malformed thumb (21). The bones of the involved limb may show disproportionate overgrowth, in part with muscular hyperplasia (21), or deficient growth (as in the present case). Contralateral polydactyly was seen in the present case.

Moreover, socket-type nose (12), scoliosis (14, 15), marked widening of the paravertebral segments of the contralateral 5th, 6th and 9th ribs (12), and abnormal bone mineralization (18) have been noted. In our patient, saddle nose and scoliosis were present.

Dental anomalies

Aloi et al. (18) described ipsilateral anodontia. In the present case the ipsilateral maxillary teeth were hypoplastic. Ameloblastoma of the ipsilateral mandibula was reported by Burck et al. (19).

Cerebral anomalies

Profound mental deficiency was described by Lausecker (21), whereas mental retardation was noted by Burck & Held (12) and in the present case. Burck et al. (19) reported a mildly enlarged third ventricle, ipsilateral optic glioma and a large psammomatous meningioma. In our patient, an unsteady gait was noted.

Miscellaneous findings

Other anomalies that were so far reported in one case only: mildly dysplastic ears (12), cataracts (12), ipsilateral lipodermoid of the conjunctiva (12), and imperforate anus (17) have also been documented. So far, we hesitate to conclude whether these defects are nosologically related to the syndrome, and the same holds true for ipsilateral epicanthus and macroglossia as noted in the present case.

Differential diagnosis

So far, the syndrome of segmentally arranged basaloid follicular hamartomas with osseous, dental and cerebral anomalies has always occurred sporadically. It should be distinguished from generalized basaloid follicular hamartoma syndrome (MIM 605827), an autosomal dominant trait characterized by a disseminated, non-segmental involvement of the skin and diffuse scalp hypotrichosis (1, 3, 11). In particular, the segmental

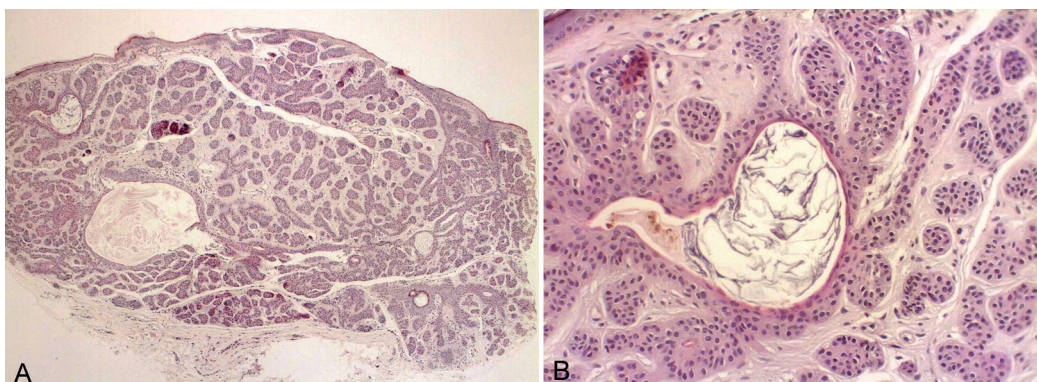


Fig. 5. Basaloid follicular hamartoma showing (A) a lacy-like pattern of anastomosing strands of basaloid cells and (B) keratin-filled cysts.

distribution of BFH that is a hallmark of the present syndrome should not be confused with a definitely non-segmental "linear arrangement" of lesions on the side of the neck as described by Wheeler et al. (3) in patients with autosomal dominantly inherited generalized BFH.

On the other hand, the syndrome described here has been misdiagnosed in the past as a unilateral manifestation of Gorlin syndrome (MIM 109400) (10), because the term *basal cell naevus* was taken as a synonym for "naevoid basal cell carcinoma" (22–24). Although it is true that multiple BFH may also be noted, intermingled with other adnexal skin tumours, in patients with Gorlin syndrome (22, 25), we emphasize that the gestalt of clinical and histopathological features of Gorlin syndrome is quite different from the syndrome described here, which is why the phenotype of Gorlin syndrome can be distinguished easily even in its mosaic forms (26). In some difficult cases (27), DNA analysis of *PTCH* may be helpful to rule out, or ascertain, Gorlin syndrome. So far, however, molecular proof of mosaicism has not been provided in such patients.

Bazex-Dupré-Christol syndrome (28) and familial multiple trichoepithelioma (2) can likewise be differentiated by their distinct histopathological features. It should be noted that hereditary multiple trichoepitheliomas (MIM 601606) have so far not been found to be associated with skeletal, dental or cerebral anomalies.

Because the papules of multiple BFH often show a comedo-like umbilication, their segmental arrangement has been mistaken for naevus comedonicus syndrome (16), although the two entities differ both clinically and histopathologically.

Names used in previous reports

So far, examples of the syndrome presented here have been described under the following names: linear unilateral basal cell naevus with comedones (14, 15, 20); systematized glandular naevus in combination with other malformations (21); unilateral linear basal cell and adnexal naevus (17); unilateral skin lesions associated with multiple neoplasms (12); unilateral skin lesions, cataracts, optic glioma and retardation: a variant of epidermal naevus syndrome? (19); unilateral linear basal cell naevus associated with diffuse osteoma cutis, unilateral anodontia, and abnormal bone mineralization (18); and naevus comedonicus syndrome (16).

Ambiguity of the terms "basal cell naevus" and "basal cell naevus syndrome"

The term basal cell naevus has been used in the past, and is applied even today, to describe numerous different phenotypes including:

- Gorlin syndrome (naevoid basal cell carcinoma syndrome) (8, 9, 22, 24, 29);
- a mosaic manifestation of Gorlin syndrome (26);
- segmentally arranged non-syndromic basal cell carcinomas of the superficial type (MIM 605462) (30–32);
- segmentally arranged non-syndromic BFH (13, 22, 33–35);
- segmentally arranged BFH with extracutaneous anomalies (14, 17, 18, 20).

This proliferation of terms has originated from the fact that Robert Gorlin himself erroneously included several cases of segmentally arranged BFH with extracutaneous anomalies (14, 17, 20, 21) as *bona fide* examples of naevoid basal cell carcinoma syndrome (10, 24, 36, 37).

From this range of different entities described under the same name we conclude that it is better to avoid the ambiguous terms "basal cell naevus" and "basal cell naevus syndrome", in order to prevent continuing confusion.

Aetiological considerations

The aetiology of the syndrome is unknown, but it can be taken as certain that it represents a mosaic phenotype. All cases so far reported were sporadic.

Grachtchouk et al. (38) assumed that a rather mild upregulation of the sonic hedgehog pathway may be aetiologically related to BFH. We emphasize, however, that mutations of *PTCH* are apparently not involved in the development of segmental BFH with osseous, dental and cerebral anomalies. No *PTCH* mutation was found in our patient.

One might speculate that this syndrome could be nosologically related to the autosomal dominant generalized basaloid follicular hamartoma syndrome (2, 11), and may represent a type 2 segmental manifestation of this disorder (39). This would explain why the segmental skin lesions of the syndrome tend to occur rather early in life (16, 18, 21) or may even be present at birth (17), and why the degree of cutaneous involvement is more pronounced than usually seen in familial disseminated BFH (14, 18, 20, 21). This hypothesis is supported by a case of segmental manifestation of non-syndromic BFH superimposed on generalized, non-segmental BFH as published by Stoof & Starink (40), and by several reports describing segmental non-syndromic BFH as a "birthmark" (6, 41–45).

On the other hand, the following arguments are at variance with this assumption. Firstly, in patients affected with the syndrome no disseminated non-segmental BFH, that would reflect a heterozygous state, have so far been noted. Secondly, no family members with dis-

seminated non-segmental BFH have been reported, as would be expected in a type 2 segmental manifestation of an autosomal dominant skin disorder (39).

In conclusion, the syndrome of segmentally arranged BFH with osseous, dental and cerebral anomalies appears to represent a distinct entity. The strikingly unilateral distribution of lesions should not be taken as an absolute prerequisite because, by way of exception, some contralateral lesions may also be noted. This mosaic disorder should always be borne in mind for differential diagnosis when a unilateral or otherwise segmental manifestation of Gorlin syndrome is discussed.

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