Naevi Spili, Café-au-lait Spots and Melanocytic Naevi Aggregated Alongside Blaschko's Lines, with a Review of Segmental Melanocytic Lesions

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This is the first case in the literature describing naevi spili, café-au-lait spots and melanocytic naevi aggregated alongside Blaschko's lines. The pattern of melanocytic lesions in our patient is different from the congenital pigmentary syndromes and the segmental distribution of melanocytic naevi, the quadrant distribution of dysplastic naevi or the partial unilateral lentiginosis which here are shortly reviewed. The distribution may be a result of a somatic mutation occurring at an early stage of embryogenesis when neural structures had already been formed. *Key words: pigmentary disorder; mosaicism; congenital syndrome.*

The differential diagnosis of syndromes with a dissemination of melanocytic naevi includes the Carney syndrome, neurocutaneous melanosis, epidermal naevus syndrome, premature ageing syndrome, occult spinal dysraphism, neurofibromatosis type I, the LEOPARD syndrome and phakomatosis pigmentovascularis. Melanocytic naevi or lentigines aggregated alongside Blaschko's lines have also been described. In this paper, we demonstrate a previously unrecognized combination of naevi spili, café-au-lait spots and melanocytic naevi aggregated alongside Blaschko's lines, and provide differential diagnostic criteria to separate the different conditions with multiple melanocytic naevi and lentigines.

CASE REPORT

A 5-year-old boy was noted to have multiple pigmented lesions characteristically distributed over the left side of his face, cervical region, chest and arm. The macules had been present since birth, increasing in size and number over time. Family history was negative.

Physical examination revealed speckled light brown pigmented areas with multiple darker brown macules (naevi spili) alongside Blaschko's lines (Fig. 1). Interestingly, an area around one Blaschko's line on the upper cheek was spared. Clinically, in addition to the large naevi spili described, café-au-lait spots on the face and smaller ones on the arm were present, and multiple flat light to dark brown plaques, 0.3 – 4 cm in diameter, sometimes with increased growth of terminal hairs, could be detected (Fig. 2). Ophthamologic examination showed astigmatism and myopia. No neurologic abnormalities could be found.

Several excisions of the brown plaques on the face and arm revealed, below a normal or papillomatous epidermis, nests of melanocytic cells without cytological atypia in the dermis. Melanocytic cells were also found more deeply around appendages and neurovascular bundles, indicating congenital melanocytic naevi.

DISCUSSION

Melanocytic naevi have been reported in association with several congenital syndromes (1). These associations are important to recognize for early intervention if necessary. The Carney syndrome (including LAMB and NAME syndromes) is a cardiocutaneous syndrome characterized by pigmented skin lesions and atrial myxomas. LAMB consists of lentigines, atrial myxomas, mucoid neurofibromas, mucocutaneous myxomas, and blue naevi; NAME consists of blue naevi, atrial myxomas, mucoid neurofibromas, and ephelides. Cardiac myxomas have to be removed to prevent congestive heart failure and embolization. Autosomal dominant and X-linked dominant inheritance have been documented for this syndrome; most cases exhibit sporadic inheritance. A mutation in the

Fig. 1. Large naevi spili, café-au-lait spots and congenital melanocytic naevi on the left side of the face alongside Blaschko's lines.

Fig. 2. Simultaneous presence of large naevi spili, smaller café-au-lait spots and congenital melanocytic naevi on the left arm of the patient.

embryonic neural crest could account for melanocytic alterations and cardiac abnormalities (2).

Neurocutaneous melanosis is characterized by multiple melanocytic naevi (> 20 cm in diameter in adults or 6–9 cm in infants) and benign or malignant melanocytic tumours of the leptomeninges. Neurocutaneous melanosis is postulated to represent a congenital error in morphogenesis of the embryonal neuroectoderm (3). Happle (4) has proposed that the condition could result from a dominant lethal gene that survives by mosaicism. The risk of malignant transformation of giant pigmented naevi ranges from 2–42% (5). Children with such pigmented naevi located on the head, neck or posterior midline, seem to be at higher risk of leptomeningeal melanosis with malignant transformation, and must be carefully monitored for early detection of neurological symptoms (6). Kadonaga & Frieden (3) diagnosed leptomeningeal melanoma in 62% of patients. The syndrome almost universally carries a poor prognosis, regardless of the presence or absence of malignancy (3).

Another syndrome with melanocytic naevi is the epidermal naevus syndrome, which consists of epidermal naevi, central nervous system abnormalities like mental retardation, seizures and hydrocephalus, skeletal defects, and neoplasms. Surveillance for the early detection of systemic malignancies and of neoplasms within the epidermal naevi (basal cell carcinoma, squamous cell carcinoma) may be required. The syndrome probably results from a somatic mutation that would be lethal if not present in a mosaic state (7). Most cases appear sporadic, but autosomal dominant transmission may occur (8).

Premature ageing syndrome and occult spinal dysraphism are also associated with congenital melanocytic naevi. The diagnosis of spina bifida occulta should be considered if neurologic defects with lumbosacral cutaneous signs like melanocytic naevi or port wine stains occur.

Neurofibromatosis type I is characterized by multiple neurofibromas, six or more café-au-lait spots, axillary freckling, and Lisch nodules. One to 15% of patients has melanocytic naevi, which supports the hypothesis that both melanocytic naevi and neurofibromas represent abnormalities of neural crest-derived cells. Neurofibromatosis type I is caused by mutation of chromosome 17 within band q11.2. Another form is segmental neurofibromatosis, characterized by segmental appearance of cutaneous neurofibromas and/or café-au-lait spots. Gerhards & Hamm (9) described a segmental neurofibromatosis without

neurofibromas. The diagnosis is based on the presence of café-au-lait spots, axillary freckling and skeletal abnormalities.

The LEOPARD syndrome (multiple lentigines syndrome) consists of lentigines, electrocardiographic abnormalities, ocular hypertelorismus, pulmonic stenosis, abnormal genitalia, retardation of growth, and deafness. Most cases have been transmitted in an autosomal dominant manner. Nordlund et al. (10) suggested the basic genetic defect in the lentigines syndrome to be of neuroectodermal origin, with secondary or pleiotropic changes in the organs derived from the mesoderm. The important issue is that the occurrence of multiple widespread lentigines, or generalized lentigines, indicates the need for a thorough physical evaluation (11).

A combination of melanocytic naevi and naevus flammeus indicates phakomatosis pigmentovascularis (12). Zahorcsek et al. (13) described a case with circumscribed lentiginosis, naevi flammei, and naevus spilus.

Melanocytic naevi also have been reported following Blaschko's lines (14). A 5-year-old boy was reported with agminated pigmented naevi in a bandlike distribution following the length of the left forearm. Histological examination revealed a junctional naevus. The same phenotype was mentioned before by Effendy & Happle in 1992 (15). The linear distribution suggests a clonal outgrowth of cells that carries a gene responsible for the development of melanocytic naevi (15). A somatic mutation in this gene probably occurred at an early stage of embryogenesis (16). Brunner et al. (17) described a woman with congenital segmental agminated melanocytic naevi in a distribution corresponding to the trigeminal dermatome, and no other congenital abnormalities.

Sterry & Christophers (18) reported a case of quadrant distribution of dysplastic naevi, lentigines and common acquired naevi. In addition, two malignant melanomas developed from dysplastic naevi within this quadrant. They also suggest a single and dominant mutation at an early stage in embryogenesis (18).

Segmental lentiginosis was first mentioned by McKelaway (19) in 1904, and refers to a rare condition with asymmetric distribution of lentigines on one side of the body. Biopsy specimen showed increased numbers of basal melanocytes and hyperpigmentation of the lower epidermis (20). Marchesi et al. (21) described a segmental lentiginosis with "jentigo" histologic pattern. The clinical diagnosis was segmental lentiginosis with the presence of dark macules with no background pigmentation, and, histologically, a combination of the lentiginous and junctional melanocytic naevus patterns were found (elongated interpapillary ridges, increased number of melanocytes, as well as some nests of melanocytes at the dermoepidermal junction).

Another pigment disorder is the zosteriform lentiginous naevus. Matsudo et al. (22) reported three cases with a diffuse, brown, non-hairy pigmented area with multiple darker brown macules in a zosteriform distribution, which can be identified as a segmental naevus spilus. Histologic examination of biopsy specimens revealed increased numbers of melanocytes in the basal layer, and the basal keratinocytes contained increased amounts of pigment. Small amounts of junctional naevus cells were seen at the tips of the papillae (22).

The above-mentioned congenital syndromes with other abnormalities were not present in our patient.

Other cases are reported, such as melanocytic naevi following Blaschko's lines (14, 15), corresponding to the trigeminal dermatome (17) or dysplastic naevi in a quadrant distribution

(18). They differ partly in the distribution and partly in the absence of naevi spili and café-au-lait spots, as well as in the presence of dysplastic naevi and malignant melanoma. Melanocytic naevi with a dermal component, as seen here, are not features of the segmental lentiginosis, the segmental lentiginosis with "jentigo" histologic pattern or the zosteriform lentiginous naevus. Careful history, physical examination and excisions may allow one to distinguish it from more serious genetic disorders. Whether the pigmented lesions may have malignant potential can only be ascertained with long-term follow-up.

The distribution of the pigmented lesions alongside Blaschko's lines in our case may suggest a clonal outgrowth of cells carrying an altered gene that is responsible for the development of various melanocytic lesions. This clone might originate from a somatic mutation occurring at an early stage of embryogenesis, when neural structures have already been formed (16).

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