Title: The Biker Glove Pattern of Congenital Melanocytic Nevi

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Abstract:
Importance: The biker glove pattern of acral infantile hemangiomas (IH) has been described, which does not correspond to known embryologic segments but rather suggests specific timing for key pathogenic events. Congenital melanocytic nevi (CMN) are common birthmarks with 20% occurring on the limbs. While advances have been made, the exact pathogenesis of CMN remains unclear.
Objective: We sought to describe a unique distribution pattern of congenital melanocytic nevus arising on the distal extremities and to explore the relationship between that pattern, limb development and CMN pathogenesis.
Design: This was a retrospective chart review of a cohort of patients from a single tertiary pediatric dermatology referral center. Medical records were reviewed for clinical data and photographs.
Setting: A single tertiary pediatric dermatology referral center.
Participants: Four patients with acral CMN with a biker glove distribution.
Main Outcome(s) and Measure(s): Clinical characteristics including morphology, distribution and complications associated with the CMN were reviewed.
Results: Four patients with CMN of varying sizes on the distal extremities demonstrated a biker glove distribution, with sparing of the distal digits.
Conclusions and Relevance: The existence of the biker glove pattern suggests that CMN arise from early mutations in melanocyte precursors and supports the hypothesis that melanocyte migration in CMN occurs in a circular field from a central point. Developmental errors in mesenchymal precursors with similar migration patterns may explain this shared pattern among CMN and IH.

Key Points:
Question: Does the biker glove pattern occur in CMN?
Findings: The 4 presented cases demonstrate the biker glove pattern among CMN of varying sizes.
Meaning: The biker glove pattern occurs in acral CMN, suggesting an early postzygotic mutation in melanocyte precursors and supporting the hypothesis that melanocyte migration in CMN emanates from a central point in a circular field.

Introduction

Congenital melanocytic nevi (CMN) affect approximately 1% of newborns[1], and occur anywhere on the body[2]. In recent years important advances have been made in the understanding of CMN pathogenesis. The causal mutations of CMN have been identified[3-5], and Kinsler and Larue have presented data suggesting the existence of 2 distinct melanocyte precursor populations, implicating precursors derived from mesoderm in the patterning of multiple CMN[6].

A "biker glove" pattern of acral infantile hemangiomas (IH) has been described, characterized by extension onto the fingers and toes with a contiguous border across digits and sparing of the distal tips[7]. This pattern did not correspond to known embryonic segments, sensory nerve distributions, dermatomes or lines of Blaschko. It was hypothesized that for the biker glove pattern to arise, the developmental error giving rise to IH must occur between 38 and 52 days gestation, after the finger rays are formed but before the interweb spaces are completely developed and the distal digits have differentiated[7].

We report 4 patients with biker glove pattern of CMN involving the hands and feet. The existence of this pattern has important implications for our understanding of the origin and migration patterns of melanocytes and the pathogenesis of CMN.

Case 1

A healthy 11-year-old girl has been followed since age 3 years for a medium-sized CMN (6 cm; M2 according to Krengel *et al.*[8] classification, projected adult size 10 cm) of the right hand (Figure 1A-B). The light-to-medium brown thin plaque extended from the dorsal wrist to the base of the 2nd digit and to the DIP on the thumb, and around to the ventral surface of the thenar eminence. There was sparing of the distal fingertip, associated hypertrichosis and slight dermal thickening. She has had no associated complications and has not had treatment.

Case 2

A 2-week-old female born full term presented with a large CMN of the right foot (circumferential, 8 cm in length; L1, projected adult size 22 cm) and multiple associated medium sized and small satellite lesions (Figure 1C-D). The nevus extended onto each

toe circumferentially with a contiguous line from one digit to the next and spared the tips of the digits. A brain and spine MRI did not demonstrate neurologic abnormalities. Her nevi have grown in proportion with her somatic growth, without significant change in color and she has not developed new satellites.

Case 3

A 3-year-old male presented with a giant CMN of the left hand, arm, chest and back with several satellites (G2, projected adult size >60 cm). His course was complicated by severe dermatitis within the CMN, necessitating excision and grafting of a large portion of the affected arm and asymptomatic neurocutaneous melanosis. He died from a melanoma arising in the central nervous system at age 11 years. Photographs taken before surgery of his arm reveal a giant nevus with sparing of the tips of all 5 fingers (Figure 2).

Case 4

A healthy 9-year-old female was followed since age 1 year for a right 5th finger medium-sized CMN (3.5 cm circumferentially; M1, projected adult size 5 cm). Her CMN remained a light brown color and extended from the MCP to the PIP joints, starting dorsally and wrapping around nearly circumferentially to the ventral surface. There was sparing of the distal fingertip. It had significant hypertrichosis, and grew proportionally with her without any complications.

Discussion

Congenital melanocytic nevi (CMN) result from post-zygotic mutations within presumed melanocytic precursor cells that divide and migrate to populate a particular

area [3,4,9], in these cases the distal limbs. All 4 cases presented had sharp cut-offs and sparing of the distal extremity in a biker glove pattern.

The biker glove pattern suggests a specific timing of pathogenic events during fetal life, distinct populations of melanocytes and possibly the existence of protective factors within the digit tips. Upper limb development begins with the appearance of the limb bud on day 24; the hand plate can be distinguished by day 33, and on day 38 finger rays develop and the interweb spaces begin to form by apoptosis. By day 52, fingers are well formed. In order for the biker glove morphology to exist with its contiguous border along multiple digits, the mutated melanocyte precursor must exist in the limb bud after the formation of the finger rays but before the interweb spaces are completely developed. It is not clear whether that precursor suffers its mutation prior to migrating into place or once present in the limb bud.

To result in a larger nevus, such as the giant CMN affecting the entire arm in case 3, the causal mutation is likely to occur in an earlier precursor cell, and conversely the medium sized CMN in case 4 must have resulted from a later mutation in a precursor that would divide to populate only a small segment of the digit. Other genetic factors may also play a role in determination of final nevus size.

The finding of a biker glove pattern in CMN lends support to the hypothesis of Kinsler and Larue that melanocyte migration in most CMN emanates from a central point, in a circular field, perhaps due to melanocyte precursor division and passive diffusion[6]. The patterns presented here correspond to the distal limb (or glove/stocking) field as described previously, with variable involvement of the digits and sparing of the finger/toe tips [6].

Neither the segmental neural crest-derived melanocyte precursors nor the newly described mesoderm-derived population of melanocytes seem to supply the digital tips and nails [6], suggesting that those structures are supplied by a yet unidentified population of melanocyte precursors. Though unlikely, it is conceivable that the melanocyte precursors in the limb bud produce a digit tip and nail precursor early on, prior to a somatic mutation. However, the presence of fingertip sparing in giant CMN makes this unlikely.

It is noteworthy that both CMN and IH both produce this same unique morphologic pattern on the extremities. The embryonic origins of IH remain unknown, in spite of much research and many theories of pathogenesis. Multipotent dysregulated progenitor-like, hemangioma-derived stem cell (HemSC) proposed to give rise to IH do express mesenchymal markers (CD90) [10]. Thus developmental errors in mesenchymal precursors with similar migration patterns may explain the shared biker glove morphology among CMN and IH both in melanocyte and endothelial (or other vascular-associated) lineages. Although controversial, reports of an association between CMN and IH could lend support to this theory[11-12].

Biker glove nevi represent a subset of divided or kissing nevi, in which nevi involve adjacent portions of mobile body parts that appear as a single nevus when those body parts are juxtaposed. Classically described as CMN on the upper and lower eyelids that appear as one lesion when the lids are closed[13], divided melanocytic nevi have also been described on the glans penis and adjacent foreskin[14] and divided epidermal nevi on adjacent fingers [15]. In all of these cases, the nevi are thought to initially arise as a single lesion at a time during embryogenesis before the two body parts separate.

The biker glove pattern in medium-to-giant sized CMN of the extremities suggests early mutations in melanocyte precursors and provides further support for the non-segmental migration pattern of some melanocyte precursors [6]. Recognition of morphologic patterns such as this may contribute to a greater understanding of melanocyte biology, the pathogenesis of CMN and IH.

Table 1. Summary of Cases

Case #	Sex	Age at presentation	Affected limb	Distribution on limb	Color	Projected Adult Diameter	Clinical characteristics of nevus	Complications	Other cutaneous lesions	Additional Medical History
1	F	3 years	Right upper extremity	Dorsal hand from wrist to base of 2nd digit, and extending onto thumb up to IP joint, thenar eminence	Light brown	10 cm (M2)	Speckled, hypertrichotic, became darker and less nodular over time	None	None	None
2	F	2 weeks	Right lower extremity	Mid-calf to DIP on all fingers, primarily dorsal, wraps around ventrally with few islands of sparing on sole	Dark brown	22 cm (L1)	Thickened and became more uniformly dark brown over time	None	Numerous small and medium sized satellites	Normal amiocentesis, Normal brain and spine MRI
3	M	3 years	Left upper extremity	Entire arm from shoulder to fingertips circumferentially	Dark brown	>60 cm (G2)	Moderate color heterogeneity and rugosity, associated hypertrichosis	Severe dermatitis; Multiple reconstructive surgeries; Died of melanoma	Numerous small satellites	Neurocutaneous melanosis
4	F	1 year	Right upper extremity	D5 MCP to PIP, nearly circumferential wrapping from dorsal to ventral	Light brown	5 cm (M1)	Hypertrichotic	None	None	None

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Figures.

Figure 1A-B) Medium CMN of Case 1 extending from the dorsal hand and wrist to the thenar eminence and distally to the interphalangeal joint of the thumb, with sparing of the distal thumb. C-D) Large CMN of the right lower leg and foot of Case 2 demonstrating a circular pattern with its central point on the dorsal foot and sparing of all distal digits.

Figure 2A-C) Giant CMN of the left upper extremity of Case 3 demonstrating sparing of all fingertips. Surgical scars are visible on the forearm.


A
B
C
D


A
B
C