Giant melanocytic nevi and soft tissue undergrowth in the left leg: Pathogenetic hypothesis

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Abstract

Congenital melanocytic nevi (CMN) are observed frequently in children. The anomalous skin shows a widely variable clinical expression not only in the anatomic location, but also in color, morphology and superficial structure. According to the width CMN are distinguished in small, medium, large or giant. Aside the cosmetic problem and its psychological implications, CMN may present with severe complications consisting of malignant transformation and/or central nervous system involvement. We report on a 3-month old infant with an extensive CMN in the left leg, which extended from the lower portion of the knee to the foot, with satellite nevi. Concomitant with the extensive nevi in the same district a remarkable reduction in size was present, and involved the adipose and muscle tissues, contributing to a counterpart diameter difference of 5 cm, without bone involvement. Melanocytic nevi and soft tissue undergrowth in the leg is a usual association; a pathogenic explanation on the anomaly involving concomitantly the skin and the underneath soft tissues is advanced.

Introduction

Melanocytic nevus is a frequent and usually benign skin anomaly. It may be congenital (*i.e.* presenting since birth or soon after) or acquired, with onset at young age. The congenital melanocytic nevi (CMN) are reported to arise between the 5 to 24 weeks of gestation as a result of abnormal melanoblasts' growth, development or migration.[1,2] CMN may present in approximately 1% of newborns and show variable clinical manifestations, not only in the size, but also in the anatomic location, the color and the morphology of the cutaneous lesion.[3] In particular: the size may vary from small (<0.5 cm) to very extensive (>20 cm); any part of the body may be involved, with prevalence of location on the posterior trunk, legs, arms, head and neck; the color may show various shades of black, brown, pink, and tan. Also, the shape may be variable, presenting round or oval with smooth, regular, well circumscribed borders, while the surface texture may present as papular, verrucous or cerebriform, with coarse terminal hair growth.[4,5] A few or numerous associate satellite nevi may be located close to the CMN or distant to the main lesion. As upper mentioned, the clinical features of CMN are various and an association with extracutaneous disorders has been widely reported.[5,6]

Complications, aside the remarkable cosmetic problems with the psychological implications, include the potentially malignant transformation of CMN and the involvement of central and peripheral nervous system of the specific body area, possibly manifesting with severe neurologic impairment.

We report on an infant with an extensive CMN covering almost totally the left leg and extending to the sole of the foot. Concomitant to the CMN, in the left leg a marked reduction in size involving the soft tissues (muscle and fat) was noticed. There is no clear explanation for the concomitant pathogenetic event that has caused both the anomalies: the congenital extensive nevus and the soft tissue undergrowth.

Case Report

This 3-month- old infant is the first child of healthy, unrelated Romanian parents. He was born at 37 weeks of gestation after a pregnancy complicated by several episodes of urinary tract infections and vomiting. The mother is a cigarettes smoker and a soft-drug addict. He was born by planned caesarean section. At birth, his weight was 2700 g, length 49 cm, and head circumference 34 cm. His family history was unremarkable for cutaneous or systemic disorders. Fetal ultrasound examination did not show growth deficiency or other anomalies. The parental physical examination was normal. The prenatal period passes without problems. The child was referred to the University Hospital Policlinico-Vittorio Emanuele of Catania, Italy, for consultation regarding an extensive skin manifestation almost totally involving the left inferior limb. At the general examination the infant was found to be in fairly good physical health. His weight was 7 kg (90th percentile), the height 62 cm (50th percentile) and the head circumference 41 cm (75th percentile). Skin examination showed the presence of a melanocytic nevus totally occupying the left leg, covering the sole of the foot. The skin anomaly was measured of 25 cm long for the left leg and 9 cm long for the sole of the foot. The length of the upper and lower limbs was symmetrical and similar to the counterpart. A remarkable reduction of the diameter (5 cm) was found in the diameter of the limb segment affected by CMN, comparing to the unaffected: diameter of the left was 12 cm, while the right was 17 cm (Figure 1).

A patchy of satellite nevi of small size was noticed on the anterior side of the sole of the foot and also in the right thigh and the right leg. Gluteal and high thighs areas were slightly pigmented and a cutaneous dimple in the left gluteal area was found. Physical examination was otherwise normal. Neurologic examination and psychomotor development were regular and appropriate

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for the age.

Ophthalmologic examination, electrocardiography and hearth, abdominal and pelvic ultrasounds were normal. Leg X-rays showed no bones anomalies and normal ossification nuclei for age (Figure 2).

Brain MRI and angio-MRI were normal. Karyotype (G banding analysis at 450 band resolution) and array-CGH testing (Human genome CGH 60 K microarray kit, Agilent Technologies, Santa Clara, CA) performed on peripheral blood were normal. Skin biopsy carried out in the left leg showed dissemination of nevi cells into deep dermis and subcutis involving vascular, adnexal, and neural structure.

At the most recent clinical follow up at the of 3 years, clinical manifestation and size of cutaneous involvement were unchanged.

Discussion and Conclusions

The boy here reported showed an extensive congenital melanocytic nevus in the left leg with a noticeable, non-progressive, underneath reduction in size involving the soft tissues but not the bone. No other anomalies upon examination nor at brain MRI were found. Clinical classification of CMN were in the past exclusively based on the size of the cutaneous anomaly measured in centimeters according to the maximal diameter. The CMN were, therefore, distinguished in: small with dimension less than 1.5 cm; medium between 1.5 and 19.9 cm; large or giant if more than 20 cm. A more recent and detailed classification has been proposed on the basis of a) the relationship between the maximal diameter and the axis perpendicular of the size b) corrected by predicted adult size (PAS) and c) by the body segment involved (head; trunk and upper extremities; lower extremities) (Table 1).[4,5] Other features in the recent classification are addressed in reporting the number of the so called "satellite nevi", anatomic location, color and morphology including roughness, presence of hairs and dermal or subcutaneous nodules.[6-8]

CMN has been suggested to arise from postzygotic somatic mutation causing a deregulation of the proteins of the mitogen-activated protein kinase (MAPK) signal transduction pathway with N-Ras Protein (NRAS) and B-Raf protein (BRAF) mainly involved.[9-14] The large or giant CMN usually show a tendency to a dermatome distribution and according the location figurative term are often used to describe the cutaneous anomaly such as "bathing trunk", "vest nevus", "shoulder stole nevus", "coat sleeve nevus" or "glove/stocking nevus nevus".[7,8] In the present proband the cutaneous manifestation may be described as a "stocking nevus". CMN associated with extracutaneous abnormalities have been uncommonly reported.

The most severe complications of CMN include the neurocutaneous melanosis (NCN) and the spinal dysraphism. NCN arises from a proliferation of nevocytes within the central nervous system. This anomaly may be asymptomatic but, in some cases, may cause severe complications such as increased intracranial pressure, hydrocephalus, seizures and motor deficit or, in rare cases, evolution to melanoma lesions. The spinal dysraphism is more frequently observed in patients with large CMN localized in the lumbosacral region and may express with different neurologic symptoms including motor, sensory or sphincter dysfunction.[15-17] Malignant complications are also a harmful complication of CMN. In particular, large and giant CMN and the presence of several satellite nevi are the worst prognostic factors for malignant degeneration. As it has been reported, the estimated lifetime risk of melanoma ranges from 1% to 5% for patients who have had small CMN while it increases to 5% to 10% for the large CMN. The occurrence under 5 years of age is a relevant risk of complications, especially in patient with large CMN.[17-19]

There is a great controversy about the type, the timing and the extension of the treatment of large and giant CMN. Several types of interventions have been proposed such as dermoabrasion, chemical peel, laser ablation and complete excision.[18-20] Early excision with insertion of skin grafting may be useful both for cosmetic reason and for reducing the risk of malignant transformation. In any case, the result in preventing the malignancy may be not reached due to not complete elimination of the nevocytes.

In the proband, the extensive CMN was associated in the same segment to remarkable reduction in size (5 cm of diameter difference) of the underneath soft tissue with no bone involvement. In a report of Ruiz-Maldonado *et al.*[20] carried out in 80 patients with CMN with diameter size of more than 20 cm, a non-progressive reduction in size was reported in 18 subjects (22,5 %). They found a diameter difference between the affected limbs and the counterpart ranged from 1 to 3 cm in circumference, while the limb length was not affected nor the bone structure at the radiologic investigation. Substitution of fat tissue by nevus cells was suggested as a cause for the reduction in size of the limb affected.

Aside the hypothesis of Ruiz-Maldonado

Table 1. Classification of congenital melanocytic nevi as reported by Levy and Lara-Corrales.[5]

Predicted adult size (cm)	
Small	<1.5
Medium	
M1	1.5-10
M2	>10-20
Large	
L1	>20-30
L2	>30-40
Giant	
G1	>40-60
G2	>60

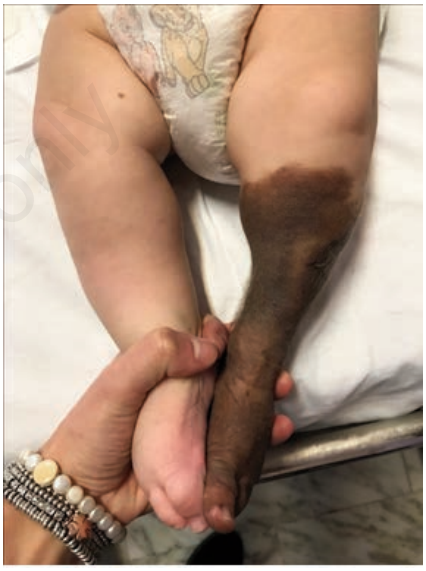

Figure 1. Patient legs. The left leg from the lower portion of the knee to the entire foot is covered by a giant melanocityc nevus. A reduction of the diameter of the left limb in comparison to the right can be also observed, especially in the area of the soleus muscle.

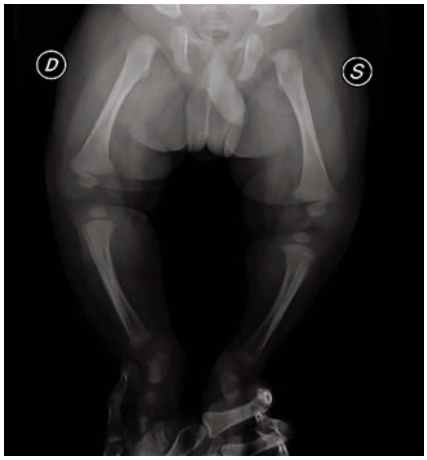

Figure 2. Lower limbs X-rays. No difference in the shape and dimension of the bone can be noticed.

et al.,[20] the concomitant skin anomaly with underneath soft tissue undergrowth is difficult to explain. We can suppose that the clinical presentation of the present and other children may be due to a single, early postzygotic mutation in MAPK pathways (involving NRAS or BRAF signaling), which could be responsible for the development of the large congenital melanocytic nevus. The massive proliferation of melanocytic cells could have caused a co-occurring minor supply of energetic substrates to the surrounding tissues (*i.e.* muscle and fat tissues), which were in close contact with the dermal mutated cells. The reduction in size did not probably involve the bone tissue because its blood supply is provided by different and deeper blood vessels.

References

1. Viana AC, Gontijo B, Bittencourt FV. Giant congenital melanocytic nevus. Ann Bras Dermatol 2013,88:863-78.
2. Elisabeth Wramp M, Langenbruch A, Augustin M, et al. Clinical course, treatment modalities, and quality of life in patients with congenital melanocytic nevi - data from the German CMN registry. J Dtsch Dermatol Ges 2017;15: 159-67.
3. Recio A, Sánchez-Moya AI, Félix V, Campos Y. Congenital Melanocytic Nevus Syndrome: A Case Series. Actas Dermosifiliogr 2017;S0001-7310;30371-4.
4. Levy R, Lara-Corrales I. Melanocytic Nevi in Children: A Review. Pediatr Ann 2016;45:e293-8.
5. Krengel S, Scope A, Dusza SW, et al. New recommendations for the categorization of cutaneous features of congenital melanocytic nevi. J Am Acad Dermatol 2013;68:441-51.
6. Price HN, O'Haver J, Marghoob A, et al. Practical application of the new classification scheme for congenital melanocytic nevi. Pediatr Dermatol 2015;32:23-7.
7. Walton RG, Jacobs AH, Cox AJ. Pigmented lesions in newborn infants. Br J Dermatol 1976;95:389-96.
8. Mallory SB. Neonatal skin disorders. Pediatr Clin North Am 1991;38:745-61.
9. Price HN. Congenital melanocytic nevi: update in genetics and management. Curr Opin Pediatr 2016;28:476-82.
10. Roh MR, Eliades P, Gupta S, Tsao H. Genetics of melanocytic nevi. Pigment Cell Melanoma Res 2015;28:661-72.
11. Charbel C, Fontaine RH, Malouf GG, et al. NRAS mutation is the sole recurrent somatic mutation in large congenital melanocytic nevi. J Invest Dermatol 2014;34:1067-74.
12. Kinsler VA, Thomas AC, Ishida M, et al. Multiple congenital melanocytic nevi and neurocutaneous melanosis are caused by postzygotic mutations in codon 61 of NRAS. J Invest Dermatol 2013;133:2229-36.
13. Wu D, Wang M, Wang X, et al. Lack of BRAF(V600E) mutations in giant congenital melanocytic nevi in a Chinese population. Am J Dermatopathol 2011,33:341-4.
14. Salgado CM, Basu D, Nikiforova M, et al. Amplification of mutated NRAS leading to congenital melanoma in neurocutaneous melanocytosis. Melanoma Res 2015; 25:453-60.
15. Lovett A, Maari C, Decarie JC, et al. Large congenital melanocytic nevi and neurocutaneous melanocytosis: one pediatric center's experience. J Am Acad Dermatol 2009;61:766-74.
16. Kinsler VA, Chong WK, Aylett SE, Atherton DJ. Complications of congenital melanocytic naevi in children: analysis of 16 years' experience and clinical practice. Br J Dermatol 2008; 159:907-14.
17. Ramaswamy V, Delaney H, Haque S, et al. Spectrum of central nervous system abnormalities in neurocutaneous melanocytosis. Dev Med Child Neurol 2012;54:563-8.
18. Roth ME, Grant-Kels JM. Important melanocytic lesions in childhood and adolescence. Pediatr Clin North Am 1991;38:791-809.
19. Shah J, Feintisch AM, Granick MS. Congenital Melanocytic Nevi. Eplasty, 16:ic4, eCollection 2016.
20. Ruiz-Maldonado R, Tamayo L, Laterza AM, Durán C. Giant pigmented nevi: clinical, histopathologic, and therapeutic considerations. J Pediatr 1992;120: 906-11.