Neurofibromatosis type 1 with progressive cribriform and zosteriform hyperpigmentation and agminated lentiginosis: a synchronous coincidence or a pathophysiological link?

Siriwan Palawisuth MD,

Chanat Kumtornrut MsC.

ABSTRACT:

PALAWISUTH S, KUMTORNRUT C. NEUROFIBROMATOSIS TYPE 1 WITH PROGRESSIVE CRIBRIFORM AND ZOSTERIFORM HYPERPIGMENTATION AND AGMINATED LENTIGINOSIS: A SYNCHRONOUS COINCIDENCE OR A PATHOPHYSIOLOGICAL LINK? THAI J DERMATOL 2016; 32: 217-223.

DIVISION OF DERMATOLOGY, DEPARTMENT OF MEDICINE, KING CHULALONGKORN MEMORIAL HOSPITAL, BANGKOK, THAILAND.

Neurofibromatosis type 1(NF1), known as von Recklinghausen disease is one of the most common neurocutaneous syndromes. NF1 is inherited in an autosomal dominant fashion with the incidence of 1 in 3,500 live births. Apart from multiple neurofibromas, its clinical manifestation is comprised of spectrum of pigmentary lesions, for example, café-au-lait macules, and flexural lentigines.

We present a case of a 27- year-old Thai male with various asymptomatic hyperpigmented lesions and skin-colored papules on his trunk since he was 5 years old.

Key words: cribriform, zosteriform hyperpigmentation, agminated lentiginosis.

From : Division of Dermatology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Corresponding author: Siriwan Palawisuth MD., email : siriwan_monk@yahoo.com

บทคัดย่อ:

ศิริวรรณ ปาละวิสุทธิ์, ชนัทธ์ กำธรรัตน์ รายงานผู้ป่วยโรค NEUROFIBROMATOSIS TYPE 1 ที่มีผื่นรอยโรคที่มีสีหลายแบบ วารสารโรคผิวหนัง 2559; 32: 218-223.

สาขาวิชาตจวิทยา ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย

Neurofibromatosis type 1 (von Recklinghausen disease) เป็นโรคทางพันธุกรรมที่มีการถ่ายทอดแบบยีนเด่น พบประมาณ 1ใน 3,500 คนและถือเป็นโรคทางระบบประสาทที่พบร่วมกับผิวหนังที่พบบ่อยที่สุดโรคหนึ่ง อาการแสดงทางคลินิกที่ตรวจพบ นอกจากจะพบ ตุ่ม neurofibroma ตามส่วนต่าง ๆ ของร่างกายแล้ว ยังสามารถตรวจพบรอยโรคที่มีสีต่างๆ กันได้ เช่น café-au-lait macules หรือ intertriginous freckling เป็นต้น

รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยอายุ 27 ปี ที่ส่งมารับคำปรึกษาที่แผนกผิวหนังด้วยเรื่องผื่นรอยโรคที่มีสีหลายแบบและตุ่มนูนที่ลำตัวโดยผื่นเริ่มเป็นตั้งแต่อายุ 5 ปี

คำสำคัญ: progressive cribriform and zosteriform hyperpigmentation, agminated lentiginosis.

Introduction

Neurofibromatosis type 1(NF1), known as von Recklinghausen disease, was first described by a German pathologist Friederich Daniel von Recklinghausen in 1882. It is the most common neurocutaneous syndrome. Diagnosis of NF1 is based on the presence of at least two of seven criteria established by the National Institute of Health Consensus Development Conference in 1988.[1] Pigmented lesions such as café-au-lait macules (CALMs), axillary freckling and agminated lentiginosis (AL) have been associated with this syndrome; however, progressive cribriform and zosteriform hyperpigmentation (PCZH) has not been reported.

Case report

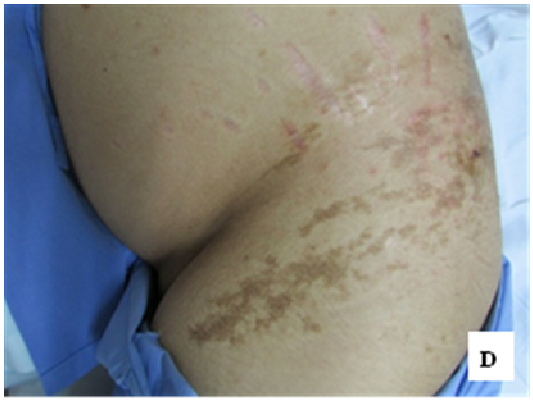
A 27-year-old male presented with progressive headache for 2 months. He had asymptomatic hyperpigmented lesions and numerous skin-colored papules on his trunk. The onset of lesions was first on the face, extending to his upper back, and then spreaded toward abdomen and left thigh. All lesions had been present since he was 5 years old and gradually enlarged with age. He denied any histories of preceding eruptions or injuries to the area. Neither family history of skin abnormalities nor concurrent medications were reported. Upon clinical examination were numerous discrete brown macules, ranging in size from 1 to 5 mm in diameter, over his left cheek with sharp demarcation at the midline anteriorly and extending bilaterally on his neck and posteriorly on the upper back (Figure. A-C). Interestingly, multiple brownish linear and oval macules arranged in zosteriform pattern on anterior side of his left thigh and lower back, which did not cross the midline were seen. (Figure. D) He also

had a few discrete skin-colored pedunculated papules on his abdomen and extremities (Figure. E). He had neither café-au-lait spots nor skin fold freckling. On ophthalmologic examination, Lisch nodules were identified in both eyes. There was no musculoskeletal involvement. Routine laboratory tests, including complete blood cell count, liver and renal function tests and serum electrolytes were normal. Magnetic resonance imaging of the brain showed an infiltrative heterogeneous enhancing mass in the left cerebellar hemisphere, without evidence of optic pathway glioma. Left paramedian suboccipital craniectomy with gross total tumor removal were performed with the histopathologic finding of an infiltrative astrocytoma of at least WHO grade III. Skin biopsies from a macule on the left side of his shoulder (Figure.C), lower back (Figure. D) and a skin-colored nodule on his abdomen also showed lentigine, basilar hyperpigmentation without nevus cells and neurofibroma, respectively (Figure. F-H) . His final diagnosis was neurofibromatosis type 1 with PCZH and AL.

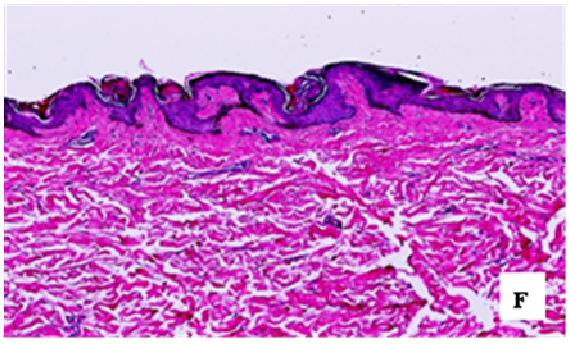


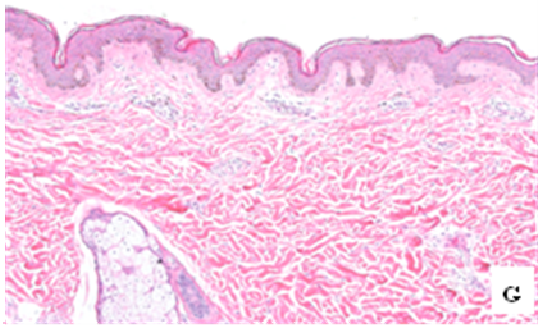


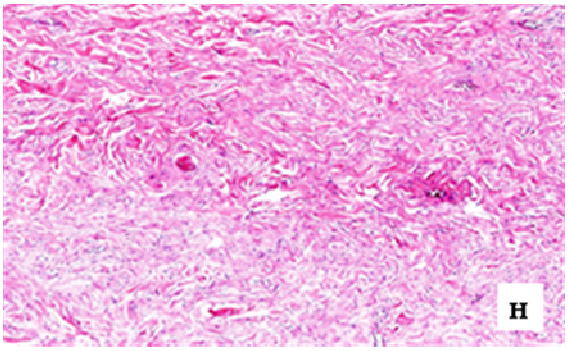












Discussion

NF1[2] is an inherited disease with autosomal dominant fashion with incidence of 1 in 3,500 live births. NF1 gene encodes the 260 kDa protein neurofibromin, considered as a tumor suppressor gene. Neural crest gives rise to two populations, dorsally and ventrally migrating cells, which are melanocytes and nervous system (schwann cells), respectively. These cells migrate through epidermis during the process of embryonic cutaneous development. It is suggested that prenatal nevi may develop from precursor for schwann cells. Also, cultured melanocytes from CALM showed a second hit mutation in the NF1 gene suggesting that the

melanocytes are the primary pathogenic cell in pigmented lesions.[3,4] Because of the variability of clinical manifestrations of NF, Riccardi, in 1982, classified NF into eight categories. Segmental NF (SNF) is NF type V that is associated with mutation of NF1 gene leading to somatic mosaicism. The common manifestations of SNF are neurofibromas, and less frequently, CALM and axillary freckling which are usually unilateral and occupy in a single dermatome. [5] Our patient was diagnosed with NF1 by the presence of multiple neurofibromas and Lisch nodules. Although skin-colored papules are predominately confined on the left side of his trunk, however those papules which across the midline to the other side of his body and the evidence of systemic involvement make his diagnosis less likely to be segmental NF.

Pigmentary cutaneous manifestations of NF1 typically present with CALMs and intertriginous freckling, Although our patient also had AL and PCZH, which had different manifestations but they might share similar etiopathogenic mechanism. AL is characterized by lentigines confined to a body segment, often corresponding to one or more dermatomes and, sometimes, involving an entire half of the body. Cutaneous lesions are located at various sites including face and neck, trunk, upper and lower limbs. The lentigines are unilateral with sharp demarcation at the midline.[5] PCZH, the late onset of linear and whorled nevoid hypermelanosis, was first described in 1978 by Rower and colleagues.[7,8,9] The following criteria were suggested:[10,11,12,13] (1) uniformly tan cribriform macular pigmentation in a zosteriform distribution; (2) a histologic pattern that consisted of a mild increase in melanin in the basal cell layer and complete absence of nevus cells; (3) no history of rash, injury, or inflammation to suggest post-inflammatory hyperpigmentation; (4) onset well after birth with gradual extension, age at onset was in the second decade of life and (5) lack of other associated cutaneous or internal abnormalities. Age of onset between birth and 54 years (77% between 1 and 15 years).[14] The trunk is the most common site of involvement.[15] The linear pigmented lesions usually follow Blaschko's lines.[12]

Hyperpigmentation in NF1 is affected by both haploinsufficiency and loss of heterozygosity of NF1 gene (Nf1+/-). Haploinsufficiency may have a role in (1) increasing the production of melanoblasts from Schwann cell precursors. (2) exhibiting higher levels of melanogenic gene expression. (3) regulating the kit-mitf signaling axis in vivo during melanocyte development and (4) increasing variation in the number and length of dendrites. However, it does not alter melanoblast survival/proliferation[15,17] which, play part in migration during embryogenesis. These

result in an unequal distribution of pigmented cells and clinical hyperpigmentation.[16]

Although the pathogenesis of both AL and PCZH in our NF1 patient have not been elucidated, they may partially share the same pathways, increase melanoblast/melanocyte numbers and dendrites from NF1gene haploinsufficiency and mosaicism. According to a new genetic concept postulated by Happle, somatic mosaicism that develops during embryogenesis leads to the proliferation and migration of two mixed populations of melanocytes with different potential for pigmentation. Both AL and PCZH affect the clonal migration and proliferation of abnormal melanoblasts during embryogenesis leading to their described clinical manifestations. From previous reports, there are very few cases of both AL and PCZH in NF1. We propose the possible pathophysiological link between abnormal types of pigmentation in NF1, however, more cases and investigations need to be studied in greater details.

กิตติกรรมประกาศ

รายงานผู้ป่วยฉบับนี้ สำเร็จลงได้ด้วยดี เนื่องจากได้รับความกรุณาจากอาจารย์ นายแพทย์ชนัทธ์ กำธรรัตน์ และศาสตราจารย์นายแพทย์ ประวิตร อัศวานนท์ ที่กรุณาให้คำแนะนำ ปรึกษาแนวคิดตลอดจนปรับปรุงแก้ไขข้อบกพร่องต่างๆด้วยความเอาใจใส่อย่างดียิ่ง มาโดยตลอดจนเสร็จสมบูรณ์ ผู้เขียนขอกราบขอบพระคุณเป็นอย่างสูงไว้ ณ ที่นี้

อนึ่ง ผู้เขียนหวังว่า รายงานผู้ป่วยฉบับนี้จะเป็นประโยชน์ต่อผู้ที่สนใจและเป็นแนวทางในการหาความรู้เพิ่มเติมต่อไปในอนาคต หากมีข้อผิดพลาดประการใดต้องขออภัยมา ณ ที่นี้ด้วย

Reference

1. Tarang G. Progressive cribriform and zosteriform hyperpigmentation: Where are we at present? Indian Dermatol Online J. 2013; 4: 264-6.
2. Pazos LR, Rodriguez-Granados MT, Toribio J. Lentiginous mosaicism and mosaic generalized neurofibromatosis type 1. Int J Dermatol. 2014; 53: 88-90.
3. Theos A, Korf BR. Pathophysiology of Neurofibromatosis Type 1. Ann Intern Med. 2006; 144:842-9.
4. Jouhilahti EM, Peltonen S, Heape AM, Peltonen J. The Pathoetiology of Neurofibromatosis 1. Am J Pathol. 2011; 178: 1932-39.
5. Michal Sobjanek, Magdalena Dobosz Kawalko. Segmental neurofibromatosis. Postepy Dermatol Alergol. 2014; 6: 410-2.
6. Micali G, Nasca MR, Innocenzi D, Lembo D. Agminated Lentiginosis: Case Report and Review of the Literature. Pediatr Dermatol. 1994; 11: 241-5.
7. Rower JM, Carr RD, Lowney ED. Progressive Cribriform and Zosteriform Hyperpigmentation. Arch Dermatol. 1978; 114: 98-9.
8. Gutte RM. Progressive cribriform and zosteriform hyperpigmentation. Indian Dermatol online J. 2014; 5: 38-40.
9. Schepis C, Alberti A, Siragusa M, Romano C. Progressive cribriform and zosteriform hyperpigmentation: The Late-Onset Feature of Linear and Whorled Nevoid Hypermelanosis Associated with Congenital Neurological, Skeletal and Cutaneous Anomalies. Dermatology.1999; 199: 72-3.
10. Cho E, Cho SH, Lee JD. Progressive cribriform and zosteriform hyperpigmentation: a clinicopathologic study. Int J Dermatol. 2012; 51: 399-405.
11. Sofie De Schepper, Joachim Boucneau, Jo Lambert, Ludwine Messiaen, Jean-Marie Naeyaert. Pigment cell-related manifestations in neurofibromatosis type 1: an overview. Pigment Cell Res. 2004; 18:13-24.
12. Choi JC, Yang JH, Lee UH, Park HS, Chun DK. Progressive cribriform and zosteriform hyperpigmentation- the late onset linear and whorled nevoid hypermelanosis. J Eur Acad Dermatol Venerol. 2005; 19: 638-9.
13. Kim JY, Oh GN, Seo SH, et al. Progressive cribriform and zosteriform hyperpigmentation. Cutis. 2015; 96: 4-5.
14. Das A, Bandyopadhyay D, Mishra V, Gharami RC. Progressive cribriform and zosteriform hyperpigmentation. Indian J Dermatol Venereol Leprol. 2015; 81: 321-3.
15. Monteagudo B, Leon-Mateos A, Campo-Cerecedo F, Cabanillas M. Progressive Cribriform and

Zosteriform Hyperpigmentation. Actas Dermosifiliogr. 2013; 104: 824-37.
16. Sofie De Schepper, Ophelia Maertens, Tom Callens, Jean-Marie Naeyaert, Jo Lambert, Ludwine Messiaen. Somatic Mutation Analysis in NF1 Café au lait Spots Reveals Two NF1 in the Melanocytes. J Invest Dermatol. 2008; 128: 1051-3.
17. Sofie De Schepper, Joachim Boucneau, Yves Vander Haeghen, Ludwine Messiaen, Jean-Marie Naeyaert, Jo Lambert. Café-au-lait spots in neurofibromatosis type 1 and in healthy control individuals: hyperpigmentation of a different kind?. Arch Dermatol Res. 2006; 297: 439-49.