Case Report

Incontinentia Pigmenti Achromians of Ito: An Ultrastructural Study

Piti Palungwachira MD, PhD*,
Pranee Palungwachira MD**

** Srinakharinwirot University Skin Center, Srinakharinwirot University*
*** Department of Family Medicine, Ramathibodi Hospital, Faculty of Medicine, Mahidol University*

A clinico-pathological and EM study of a Thai boy with hypomelanosis of Ito, one of the neurocutaneous syndromes, is reported. At birth, typical skin hypopigmentation on the trunk and a hypopigmented streak on the left lower extremity were noted. Associated cutaneous pathology shows a decrease of melanin granules within basal and malpighian keratinocytes. Ultrastructural studies highlight a normal appearance for basal and malpighian keratinocytes, but a lack of melanosomes in the malpighian cells. Melanosomes are also dramatically reduced in the basal keratinocytes, which appear small, single or clustered and surrounded by a membrane. Melanocytic degeneration has been observed and dendritic melanocytes contained various stages of nonmelanised (stage II), partially melanised premelanosome (stage III) and rarely stage 4 melanosomes. The authors observed an increase in the number of Langerhans cell which have not previously been described. There were unmyelinated axon of nerve containing melanosomes at the dermoepidermal junction. The significance of these findings will be worthwhile to note that abnormal nerve termination in close relationship with basal keratinocyte, degenerated melanocyte, premelanosomes and langerhans cell are important in explaining the pathogenesis of Hypomelanosis of Ito.

Keywords: *Hypomelanosis of Ito (incontinentia pigmenti achromians), Ultrastructural study*

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Hypomelanosis of Ito (HI) or incontinentia pigmenti achromians is a rare multisystemic neurocutaneous disorder, consisting of hypopigmented, macular streaks and whorls in a blaschkoid distribution[1]. However, it has been suggested that the condition is greatly under reported due to the difficulty in detecting the hypopigmented areas without the use of a Wood's lamp in fair skinned individuals[2]. This case, to the authors' knowledge, is the first documented report on clinico pathological and EM study in Thailand.

Case Report

A 5-year-old boy with hypomelanosis of Ito (HI) presented on the 4th day of life with hypopigmented streaks and whorls following the lines of Blaschko on the back, the arms and the legs (Fig. 1). In addition, patchy depigmented areas were present on the trunk. The hypopigmentaion was more pronounced on examination by Wood's light. There was no history of bullous, verrucous or hyperpigmmented lesion. No known abnormality existed in either parent or any other family members. There were no known neurological or other abnormalities. The diagnosis of hypomelanosis of Ito without systemic manifestations was made on a clinical basis.

Correspondence to : Palungwachira P, Srinakharinwirot University Skin Center, Srinakharinwirot University, Sukhumvit 23, Bangkok 10110, Thailand.

Light and Electron microscopy

The cutaneous hypomelanotic lesion was excised and examined by light and electron microscopy. The tissue for light microscopy was fixed in formalin and embedded in paraffin, and 4 μm sections were stained with hematoxylin and eosin, dopa and giemsa stain. For routine electron microscopic observation, tissues were fixed in 2.5 per cent glutaraldehyde buffered with phosphate (pH 7.4) at 4° C and postfixed

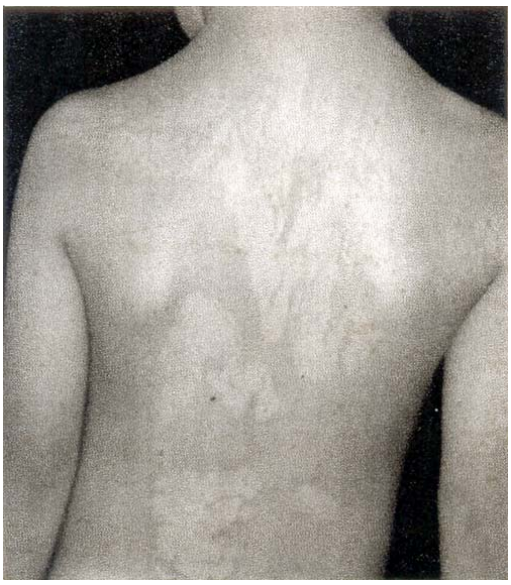

Fig. 1 Bizarre hypopigmentation following Blaschko lines occur on the trunk

in 1 per cent osmium tetroxide in the same buffer for 1 h. After dehydration in a series of graded concentrations of alcohol, the tissues were embedded in Epon. The 1 μm semi-thin sections were stained with toluidine blue to select appropriate areas for study. Ultrathin sections were cut by an ultratome with a diamond knife, double stained with uranyl acetate and lead citrate, and examined and photographed under an electron microscope (H-600, Hitachi) at an accelerating voltage of 75 kV.

Results

Light microscopy

Histopathological findings showed the melanocytes in the depigmented areas was slightly reduced in number. There was a decrease of melanin granules within basal and malpighian keratinocytes and a lack of pigmented cells in the upper dermis; perivascular lymphohistocytic cellular infiltrates can be present (Fig. 2). The melanocytes in the basal layer showed weakly positive dopa reactions. Giemsa stain revealed normal numbers of mast cells in the dermis.

Electron microscopy

TEM of the hypopigmented macule revealed epidermal keratinocytes of the involved skin contained melanosomes of stage IV, which grouped to make melanosome complexes or existed as a single body. These melanosomes, however, were rather small in size and decreased in number. Abnormal keratinization was not observed. The number of melanocytes did not seem to be decreased, but TEM showed reduced pigment formation evidenced by the presence of stage II, III melanosomes. Each melanocyte generally contained only a few small melanosomes and regressive alterations (i.e. a marked vacuolization) were found in close proximity with keratinocytes showing similar regressive changes and decreased in number of melanosomes (Fig. 3). The cytoplasm of these cells contained a few

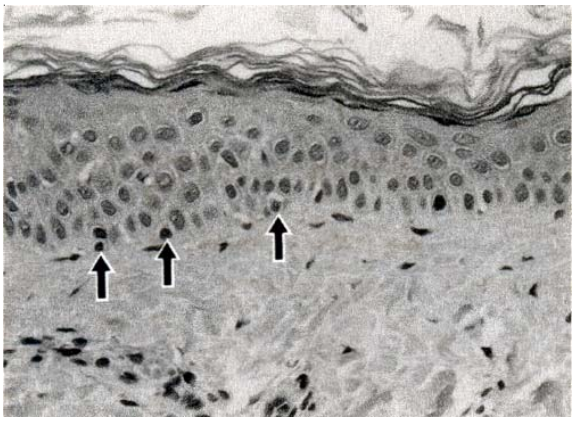

Fig. 2 Slight hyperkeratosis and partial decrease of melanin pigment in melanocyte (➜) in the basal layer. (H&E x 160)

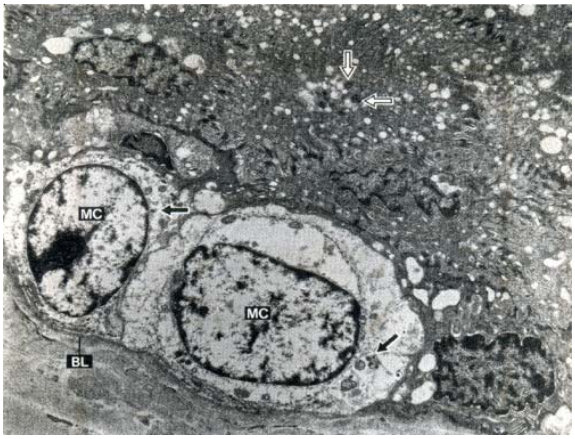

Fig. 3 Regressive changes of melanocytes and normal keratinocytes. Two melanocytes (MC) with decrease of cytoplasmic organelles, decrease in amount of melanosome and prominent vacuolization are associated with keratinocyte. Keratinocyte contains small melanosome aggregates (⇨). (BL= Basal lamina, → melanosome in melanocyte, ⇨ small melanosome aggregate in keratinocyte, x 5,900)

organelles: rough endoplasmic reticulum was scarce and the Golgi apparatus was in variable quantity, but the most distinctive features of the melanocytes were the reduced number and size of the melanosomes, prevalent in the stages II and III (Fig. 4). Moreover, the melanocytes showed evident intermediate filaments. An interesting finding was the apparent increase of melanocyte surface directly faced with the basal lamina. The melanocytes showed cytoplasmic projections and the cytoplasm of the dendritic processes contained nonmelanised (stage II), partially melanised premelanosomes (stage III) and melanosomes (stage IV) (Fig. 5) as compared with the control site. A gradient of severity of melanocytic degeneration had been observed increasing from the periphery to the centre of the hypopigmented lesion, and the main features were cytoplasmic vacuolization, aggregation of melanosomes, autophagic vacuoles and fatty degeneration. A more careful observation demonstrated Langerhans cells frequently associated with the presence of lymphocytes with indented nuclei lying among the keratinocytes (Fig. 6). The dermis demonstrated un-

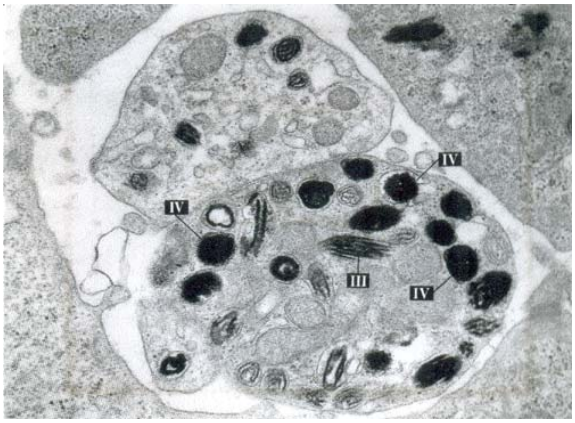

Fig. 4 Cytoplasm of melanocyte contains a small number of ellipsoidal non melanised melanosome (II) and partially melanised melanosome (III) (x 18,000)

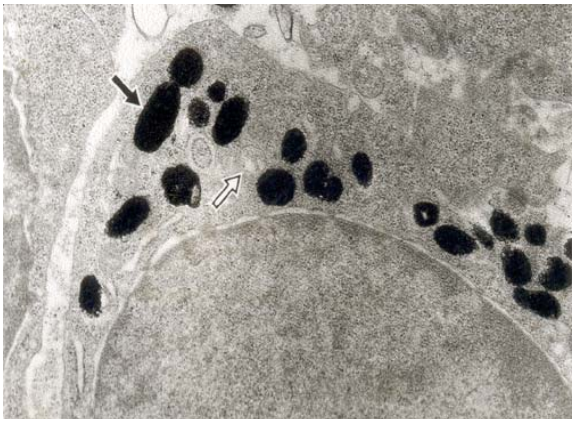

Fig. 5 A dendritic process contained nonmelanised, partially melanised premelanosomes (III) and melanosomes (IV) at various stages (x 38,000)

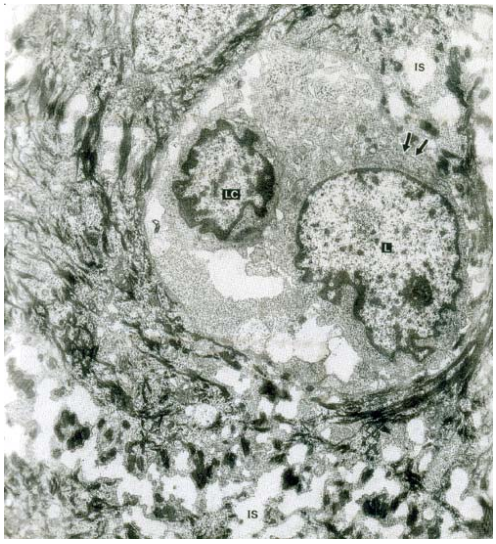

Fig. 6 Langerhans cell (L) lie in close apposition with lymphocyte (LC) among the keratinocyte, and widening of the intercellular space (IS), Birbeck's granule in Langerhans cell (→), (x 16,000)

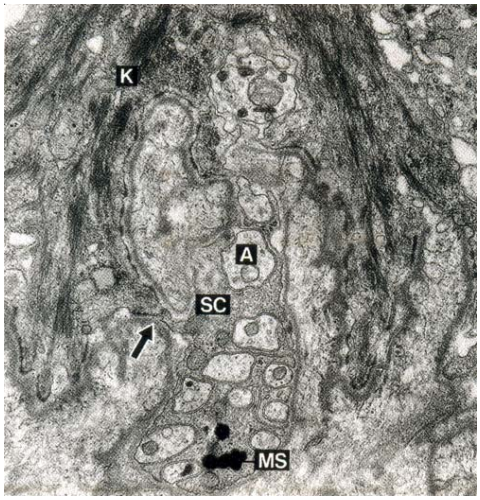

Fig. 7 Nerve fibers in the dermis. An unmyelinated axon (A) in close relationship with the basal keratinocytes (K) lie at the dermo-epidermal junction (→). The number of melanosomes profiles is reduced. SC = Schwann Cell, MS = melanosome in unmyelinated axon (x 32,000)

remarkable changes except occasional lymphocyte perivascular infiltrates. There were unmyelinated axons of nerve fibers containing melanosomes attached to the epidermis. They were reduced in number but did not show structural abnormalities. Nerve fibers were regularly surrounded by normally-looking Schwann cells (Fig. 7) and there was no increase of mast cells in the upper dermis.

Discussion

In 1952, Ito[3] first described the condition consisting of the association of hypopigmentations with systemic aberrations. Comprehensive reviews [4,5] demonstrated that this hypomelanosis can be classified as being with or without systemic involvement[6]. In the case of a hypomelanosis of Ito without systemic involvement, confusion can arise about the differential diagnosis with a generalized naevus depigmentosus. As in the presented case, this diagnosis had to be considered. However, a generalized naevus depigmentosus is mostly a unilateral hypopigmentation that is present from birth and remains stable thereafter[7]. Because the depigmentation occurred in childhood, with the involvement of the limbs with hypopigmentation along the lines of Blaschko, the authors diagnosed hypomelanosis of Ito without systemic involvement. Examination with Wood's lamp, however can enhance the visualization and improve the detection[8]. Light microscopic observations of the hypopigmented area in Hypomelanosis of Ito reveal normal histology with a relative decrease in the number and size of the epidermal melanocytes[9]. These melanocytes show a weak DOPA reaction. Occasionally, vacuolisation of the keratinocytes may be seen.

As already described by other authors[10-12], the melanocytes, at the ultrastructural level, showed an evidently decreased functional activity. Moreover, an abnormal transfer of weakly melanized melanosome to keratinocyte was also evident[13]. The apparent correlation of the hypopigmentation with a local loss of functioning melanocytes is confirmed in the authors' observations. Normally pigmented keratinocytes, can be detected in relation with preserved melanocytes, whereas in the hypopigmented zones regressive changes of melanocytes associated with similar changes of the neighbouring keratinocytes were found. This could reflect an early stage in the pathogenesis of the hypopigmented lesions, whereas in the majority of fields the melanocyte profiles are simply absent. Regressive changes of melanocytes, a reduction of the cytoplasmic processes and a tendency towards a circular contour could account in part for their basal location. The presence of dendritic melanocytes which contained nonmelanised (stage II), partially melanised premelanosomes (stage III) and melanosomes (stage IV) in the presented case suggested the hypoactivity of melanin production. The role of the dermal nerve is not sufficiently explored, it is conceivable that neurotransmitters could act on the phenotypic expression of the various cells lying in the dermoepidermal microenviroment. Morohashi et al[14] suggested that close contact between melanocytes and nerve fibers was important in explaining the pathogenesis of the disease. The present study showed melanosome within a non myelinated axon in close relationship with the basal keratinocyte at the dermoepidermal junction. In this connection it would be worthwhile to note that abnormal nerve termination stimulated by close contact with degenerated melanocytes, keratinocyte and premelanosomes could result in the formation of hypochromatic areas by an inhibitory signal carried by nerve endings. The present investigation, thus, suggested that the hypomelanosis in IPA was not related to a reduction of the number of melanocytes but also related to hypoactivity of melanin production and abnormal transfer of weakly melanised melanosomes from melanocyte to keratinocyte. An increase in the number of Langerhans cell in the present case has not previously been described, the meaning of which could be associated with the immunologic suppression of eumelanin synthesis or melanocyte metabolism. At present, however, the cause of this pigmentation alteration and increase in number of Langerhans cell in the suprabasal layer remains unresolved and needs further investigation.

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จุลทรรศน์อิเล็กตรอนในผู้ป่วยโรค *Incontinentia pigmenti achromians (Ito) 1 ราย*

ปิติ พลังวชิรา, ปราณี พลังวชิรา

ได้ทำการศึกษาจุลทรรศน์อิเล็กตรอนในผู้ป่วยเด็กไทยซึ่งได้รับการวินิจฉัยว่าเป็น Incontinentia pigmenti achromian ซึ่งเป็นโรคที่มีความสัมพันธ์เกี่ยวข้องระหว่างผิวหนัง และอาการทางระบบประสาท ลักษณะทางคลินิกพบผื่นขาวบริเวณลำตัวและบริเวณขาซ้าย จุลพยาธิวิทยาพบปริมาณเมลานินลดน้อยลงใน keratinocyte บริเวณชั้น basal และ malpighian จุลทรรศน์อิเล็กตรอนพบเซลล์ keratinocyte มีลักษณะปกติ แต่เมลาโนโซมมีขนาดเล็กอยู่โดดเดี่ยวหรืออยู่เป็นกลุ่มล้อมรอบด้วยเมมเบรน พบลักษณะของเมลาโนไซต์ถูกทำลาย เมลาโนโซมประกอบด้วยพรีเมลาโนโซมระยะ 2, 3 และเมลาโนโซม ซึ่งมีปริมาณลดลง พบพรีเมลาโนโซม และเมลาโนโซม ระยะต่าง ๆ ตรงบริเวณ dendrite ส่วนภายใน unmyelinated axon ตรงบริเวณรอยต่อระหว่างหนังกำพร้า-หนังแท้ สามารถพบเมลาโนโซม นอกจากนั้นยังพบการเพิ่มจำนวนของ Langerhans cell ซึ่งไม่เคยพบรายงานของลักษณะเช่นนี้มาก่อน การพบลักษณะดังกล่าวสามารถอธิบายความสัมพันธ์ระหว่างเมลาโนไซต์ซึ่งถูกทำลาย, keratinocyte, unmyelinated axon, พรีเมลาโนโซม และเซลล์ Langerhans ทั้งหมดอาจมีส่วนเกี่ยวข้องในพยาธิสภาพของการเกิดผื่นขาวในโรค Hypomelanosis of Ito