Case Report

Congenital Self-Healing Reticulohistiocytosis Presented with Multiple Hypopigmented Flat-Topped Papules: A Case Report and Review of Literatures

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Congenital self-healing reticulohistiocytosis, also known as Hashimoto-Pritzker disease, is a single system Langerhans cell histiocytosis that typically presents in healthy newborns and spontaneously regresses. In the present report, we described a 2-month-old Thai female newborn with multiple hypopigmented flat-topped papules without any internal organ involvement including normal blood cell count, urinary examination, liver and renal functions, bone scan, chest X-ray, abdominal ultrasound, and bone marrow biopsy. The histopathology revealed typical findings of Langerhans cell histiocytosis, which was confirmed by the immunohistochemical staining CD1a and S100. Our patient's lesions had spontaneously regressed within a few months, and no new lesion recurred after four months follow-up.

Keywords: *Congenital self-healing reticulohistiocytosis, Congenital self-healing Langerhans cell histiocytosis, Langerhans cell histiocytosis, Hashimoto-Pritzker disease, Birbeck granules*

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Langerhans cell histiocytosis (LCH) is a clonal proliferative disease of Langerhans cell involving multiple organs, including skin, which is the second most commonly involved organ by following the skeletal system[1]. LCH has heterogeneous clinical manifestations, ranging from benign single system disease to fatal multisystem disease[1-3]. LCH is classified into four unique but clinical overlapping variants, (1) Letterer-Siwe disease, an acute form of diffuse cutaneous LCH with multisystem involvement, (2) Hand-Schuller-Christian disease, a chronic progressive form with a triad of exopthalmos, diabetes insipidus and bony lesions, (3) eosinophilic granuloma, typically presents with asymptomatic granulomatous lesions of the bones, with rare cutaneous manifestation, and (4) congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease) which is characterized by congenital onset, limited cutaneous involvement and spontaneous regression.

The authors reported a case of congenital self-healing reticulohistiocytosis presenting with multiple hypopigmented flat-topped papules, which is a rare manifestation.

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Case Report

A 2-month-old Thai female infant presented with multiple hypopigmented flat-topped papules since the age of two weeks without preceding erythematous papules or vesicobullous lesion (Fig. 1A-C). The papules started on the trunk and gradually expanded to both extremities. Fever, weight loss, polyuria, or other systemic symptoms were not found. She was born at 38 weeks' of gestation by caesarean section due to gestational hypertension. Her mother had no contributory family history and no systemic drug used during pregnancy. Physical examination revealed a well-being infant with multiple discrete well-circumscribed flat-topped 5 to 10 mm hypopigmented papules distributed over her trunk and extremities, with ill-defined erythematous maculopapular rash at abdominal wall. Other physical findings were unremarkable including mucous membrane, lymph nodes, liver, and spleen. The initial differential diagnoses included tinea versicolor, flat wart and clear cell papulosis. KOH preparation from hypopigmented papules was performed with negative result. Skin biopsy, from a hypopigmented papule on right inner

thigh, revealed the aggregation of mononuclear cells with kidney-shape nucleus, or Langerhans cells, in the papillary dermis with focal epidermotropism. Focal epidermal acanthosis with mild spongiosis was also seen. No eosinophils or multinucleated giant cells were detected in the specimen (Fig. 2). Immunohistochemistry analysis was positive for CD1a and S100 protein, which confirmed Langerhans cells (Fig. 3). We subsequently referred the patient to pediatric hematologist for systemic investigation. Complete blood cell count, blood chemistries, and urinary examination were normal. Chest X-ray, abdominal ultrasound, and bone scan were unremarkable. Bone marrow biopsy demonstrated normocellular marrow. The patient was closed observed and the skin lesions completely regressed without scar within several months. The recent examination, done at the age of six months (Fig. 1D-F), showed no lesions with normal physical examination and development. Ultimately, our patient was diagnosed with a congenital

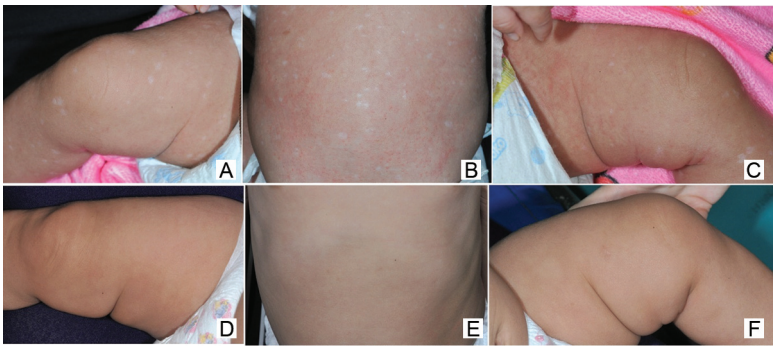

Fig. 1 (A-C) Multiple discrete flat-topped papules on trunk and extremities at the age of two months, (D-F) at the age of 6 months, all cutaneous lesions resolved.

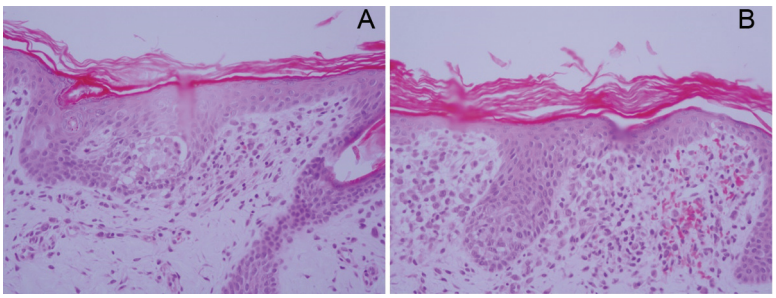

Fig. 2 (A-B) Skin biopsy specimen showing aggregation of histiocytic cells with kidney-shape nuclei in papillary dermis and focal epidermal invasion (hematoxylin-eosin stain; original magnifications: 40x).

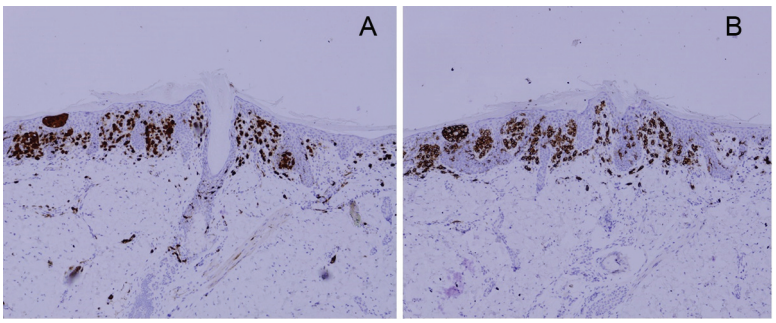

Fig. 3 Immunohistochemistry showing positive staining with S100 (A) and CD1a (B) (original magnifications: A, 20x; B, 20x).

self-healing reticulohistiocytosis according to histologic findings and clinical course. Although the patient had no systemic involvement, long-term careful monitoring was anticipated.

Discussion

Langerhans cell histiocytosis (LCH) develops in children at age of one to three years, although it can occur at any age with male to female ratio of nearly 2:1. The disease manifestation ranges from asymptomatic single organ involvement to progressive multiorgan diseases. Although the exact pathogenesis is unknown, genetic factors, viral infection, immune system dysfunction have been shown to have a role in dysregulated proliferation of histiocytes[3]. There has been a debate whether LCH is a reactive or neoplastic process. Neoplastic idea is supported by a clonal proliferation of Langerhans cells, the findings of chromosomal instability and myelodysplastic co-occurrence, whereas reactive hypothesis is supported by high differentiation of Langerhans cells, histological granulomatous lesions similar to infection and the possibility of spontaneously resolution[3]. Definitive diagnosis requires findings of characteristic Langerhans cells in H&E stained section and positive staining of CD1a and/or Langerin (CD207), as seen in our patient[1].

Congenital self-healing reticulohistiocytosis (CSHRH), also known as congenital self-healing LCH, self-regressing LCH or Hashimoto-Pritzker disease, was first described in 1973 by Hashimoto and Pritzker[4]. It is the most favorable variant of LCH. Although the definitive diagnostic criteria for CSHRH has not been proposed, the disease is characterized by (i) cutaneous lesions seen at birth or perinatal period, (ii) the occurrence in healthy newborns without systemic involvement, (iii) a spontaneous regression, (iv) the presence of large mononuclear cell or multinucleated histiocytes, and (v) 10-25% of Birbeck-granules containing histiocytes seen by electron microscope. The incidence of the disease may be under-reported due to spontaneous resolution and under-recognition. So far, approximately 150 cases were reported in English literatures[5-12]. The onset of disease was at birth or shortly after birth in most cases, but the late onset form has also been reported with the age range of 1 month to eight years[5,9,13].

Cutaneous presentations are highly diverse, but the most common presentation is multiple erythematous to purplish-brown papulonodules with or without crust and ulceration[2,4,5,9]. Hemorrhagic vesicles/bullaes[5,9,10], hemangioma-like[14], Blue-berry muffin like[5,15], umbilicated papules[16], large tumor mass[17], and hyperkeratotic palmoplantar lesions[2] have been sporadically reported. A solitary lesion, presented with a papule, or nodule with or without ulceration was reported in about 25% of cases with no predilection site[5,7,11,18,19]. It is less commonly found on mucous membrane[5,20]. LCH presented with generalized atypical multiple hypopigmented flat-topped papules with head sparing, like on our patient, has been scarcely reported. Battistella et al reported four cases of LCH with hypopigmented macules predominantly on trunk and scalp[2]. Longaker et al[20] reported a case of a 3-month old Oriental boy with relapsed numerous slightly atrophic hypopigmented macules on the trunk and extremities, which sites were not corresponding to the initial vesicopustular lesions. A skin biopsy from hypopigmented lesion confirmed LCH, lesions spontaneously resolved by 11 months. CSHRH with hypopigmented atrophic lesion has been quoted by Hashimoto et al[4], as transient cutaneous sequelae. Our case is the third case report of CSHRH in Thailand that have different presentation. The first case presented with numerous brownish red nodules scattering over both palms and soles, left thigh, abdomen, chin, and left upper eyelid and a large tumor mass on the right sole since birth, which gradually ulcerated and eventually resolved without internal organ involvement[17]. Whereas the latter case revealed diffused dark red papules on scalp, eye lid, palm and sole with systemic involvement of hepatomegaly and lung cyst[8].

Histology of CSHRH can be identical to other variants of LCH, in which Langerhans cells, containing reniform (kidney-shaped) nucleus, infiltrate papillary dermis and sometimes invade overlying thinning or ulcerated epidermis. Langerhans cells in the dermis often admixed with variable degree of eosinophils, lymphocytes, and neutrophils. Some reports showed that the infiltration could involve deeply into the subcutis[21]. Langerhans cells are stained positive to CD1a, S100, Langerin (CD207), ATPase, peanut lectin, α-D-mannosidase, but negative for CD68 (the macrophage marker), and factor XIIIa (the dermal dendrocyte marker). Langerin (CD207), a highly specific Langerhans cell marker, is an endocytic receptor that functions as an inducer of Birbeck granule formation[18]. Although indeterminate cell histiocytosis is also stained positive to S100 and CD1a, the histology of these cells fail to show

characteristic kidney-shape nucleus, and they are also stained positive for macrophage marker. In CSHRH, Birbeck granules can be found in 10 to 25% of the histiocytes under electron microscopy[4,18], which no longer needed for diagnosis due to Langerin staining correlation is easier to do.

Several studies tried to distinguish a localized cutaneous form of LCH from disseminated variants by using histology and immunohistochemistry such as the loss of E-cadherin, Ki-67 expression as possible markers for disseminated diseases, and the presence of eosinophils and higher degree of necrosis as markers for limited diseases. However, the study of Kapur et al showed no significant differences in histologic findings and immunohistochemical stainings[19].

CSHRH lesions typically involute within three months with hypo or hyperpigmentation, milia, atrophic or anetoderma like lesions[5,20,22]. Although CSHRH is considered a benign, single organ involvement and self-resolving variant, its overlapping nature to other LCH variants suggests a cautious approach and long term follow-up for a future relapse and/or a development of systemic involvement. A relapse of cutaneous manifestation[2,20,21] after the initial regression or subsequent visceral organ involvement including lungs[8-10], eyes[6], or bones[9,15] involvement have been described, especially in the first year of life. Those lesions, however, eventually resolved. According to Histiocyte Society guidelines, careful physical examination, hematologic and coagulation studies, liver function tests, urine osmolality, skeletal radiographic survey, and chest radiography should be included in the mandatory investigation at the time of diagnosis and reactivation of diseases[1]. Every patient should be followed at least five years after the last disease reactivation or until final growth and pubertal development have occurred[1].

There is no specific treatment of CSHRH, but observation and long term follow-up are recommended. If lesions persist, topical corticosteroids, tacrolimus, or nitrogen mustard can be used, or localized lesions may be excised[1,3].

Conclusion

Congenital self-healing reticulohistiocytosis is a benign end of highly heterogeneous Langerhans cell histiocytosis, which is characterized by a limited cutaneous involvement and a tendency toward spontaneous resolution. However, long-term follow-up is mandatory due to its overlapping natures with other LCH diseases.

What is already known on this topic?

CSHRH can present with various types of cutaneous manifestation, disseminated lesions or less common solitary lesion.

What this study adds?

Our patient presented with multiple hypopigmented flatted-top papules, which is atypical presentation of CSHRH.

Potential conflicts of interest

None.

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ผู้ป่วยโรค congenital self-healing reticulohistiocytosis ที่มาด้วยผื่นขาว: รายงานผู้ป่วยและทบทวนวรรณกรรมทางการแพทย์

รวิพันธุ์ เอื้อรัตนวงศ์, ธนวัฒน์ คูถิรตระการ, ปุณวิศ สุทธิกุลณเศรษฐ์, อัจจิมา อิสสระ, ปิ่นนรี ขัตติพัฒนพงษ์

Congenital self-healing reticulohistiocytosis หรือ Hashimoto-Pritzker disease เป็นโรคในกลุ่ม Langerhans cell histiocytosis ที่มีลักษณะเฉพาะตัวคือเกิดในทารกที่สุขภาพแข็งแรง และสามารถหายเองได้ รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยทารกหญิงไทยอายุ 2 เดือน ที่มาด้วยรอยโรคผื่นขาวทั่วตัวโดยไม่มีตุ่มแดงหรือตุ่มน้ำนำมาก่อน ตรวจร่างกายระบบอื่นอยู่ในเกณฑ์ปกติ ลักษณะจุลพยาธิวิทยาเข้าได้กับโรค Langerhans cell histiocytosis ชัดเจน ยืนยันด้วยการย้อมพิเศษชิ้นเนื้อพบว่าให้ผลบวกต่อ CD1a และ S100 ตรวจเพิ่มเติมพบเม็ดเลือด ค่าการทำงานตับและไต ผลปัสสาวะ เอกซเรย์ปอด อัลตราซาวด์ช่องท้อง bone scan ผลการตรวจไขกระดูกอยู่ในเกณฑ์ปกติ ผื่นของผู้ป่วยหายเองโดยไม่ทิ้งรอยหรือแผลเป็นภายในเวลา 2-3 เดือน ขณะนี้ยังคงติดตามผู้ป่วยเป็นระยะ และยังไม่พบการกลับเป็นซ้ำหรือความผิดปกติของระบบอื่น ๆ