Interdepartmental Conference

A Man with Chronic Recurrent Ulcers at the Axillae and Groins

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Abstract : Langerhans cell histiocytosis is an uncommon disease. There are various skin manifestations of this disorder. We report a 15 year-old patient with Langerhans cell histiocytosis, who first presented with polyuria, polydipsia and right elbow pain. A few years later, he developed chronic recurrent ulcers at his axillae and groins, simulating hidradenitis suppurativa. Histopathology and ultramicroscopic study showed Langerhans cells infiltrating the lesions. He also had fingernail changes without any evidence of fungal infection. Hidradenitis suppurativa-like lesions with nail changes are rare manifestations of this disorder.

เรื่องย่อ : **ผู้ป่วยชายมีแผลเรื้อรังที่รักแร้และขาหนีบ**

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โรคแลงเกอฮานส์เซล ฮิสทิโอซัยโตสิส เป็นโรคที่พบได้ไม่บ่อย โรคนี้มีอาการแสดงทางผิวหนังได้หลายชนิด คณะผู้เขียนขอรายงานผู้ป่วย 1 รายเป็นโรคแลงเกอฮานส์เซล ฮิสทิโอซัยโตสิส ชายอายุ 15 ปี มีอาการนำคือถ่ายปัสสาวะบ่อย ดื่มน้ำมาก และปวดบริเวณข้อศอกขวา หลังให้การวินิจฉัยโรคได้ 3 ปี ผู้ป่วยมีแผลเรื้อรังบริเวณรักแร้และขาหนีบทั้ง 2 ข้าง ลักษณะรอยโรคที่ตรวจพบคล้ายโรคฮัยดราดีไนติส ซับเพอร์ราทิวา ผู้ป่วยได้รับการตัดชิ้นเนื้อบริเวณรอยโรค ผลทางพยาธิวิทยาและการศึกษาด้วยกล้องจุลทรรศน์อิเลคตรอนพบเซลล์แลงเกอร์ฮานส์จำนวนมากในรอยโรค ผู้ป่วยมีความผิดปกติของเล็บมือซึ่งไม่พบหลักฐานของการติดเชื้อราที่เล็บ แผลลักษณะคล้ายโรคฮัยดราดีไนติส ซับเพอร์ราทิวาร่วมกับเล็บผิดปกติ เป็นลักษณะทางคลินิกที่พบได้น้อยมากในผู้ป่วยโรคแลงเกอฮานส์เซล ฮิสทิโอซัยโตสิส

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INTRODUCTION

Langerhans cell histiocytosis (LCH) is an uncommon disease which is characterized by abnormal proliferation and infiltration of Langerhans cells. LCH can involve many organ systems but it primarily affects bone, skin, lymph node, lung, liver, spleen, endocrine gland and nervous system.[1,2] Various skin manifestations of LCH have been reported such as seborrheic dermatitis-like papules, papulonodular, xanthomatous eruption, petechiae and ulcers.[3-7] We describe a case of LCH who presented with an uncommon skin manifestation resembling hidradenitis suppurativa with nail changes.

CASE REPORT

In June 1997, a 10-year-old Thai boy presented with polyuria, polydipsia and frequent nocturia of 2-month duration. He also had right elbow pain. He was admitted to the hospital and was given a water deprivation test, which suggested central diabetes insipidus. A bone survey revealed osteolytic lesions at proximal metaphysis of right radius. Bone curettage was done at the head of the right radius. Histopathology showed Langerhans cells infiltrating the bone. He was diagnosed with Langerhans cell histiocytosis and was treated with vasopressin nasal spray, cranial radiation and chemotherapy using an induction phase of prednisolone, vinblastine, methotrexate, cyclophosphamide, and a maintenance phase of oral 6 mercaptopurine, methotrexate and cyclophosphamide. A consolidation phase of chemotherapy was planned but the patient was lost follow up.

In September 2002, he returned to the hospital with chronic recurrent ulcers at both axillae and groins of 2-year duration. These lesions first appeared as papules and plaques which spontaneously ulcerated producing a sinus tract with a yellowish discharge. The lesions began at the axillae and then progressed to both groins. He had attended many clinics and had been treated with various oral antibiotics and wound care but the lesions had not improved. He continued to use vasopressin nasal spray to control his polyuria. However he still needed to urinate about 10 times a day and drank 5 liters of water a day. He had also gained 50 kilograms weight in 5 years.

Physical examination showed an obese man who weighed 110 kilograms. He had a small penis, small testes and loss of pubic hair. Examination of the skin at both axillae and groins showed erythematous papules, nodules and plaques with ulceration and sinus tract formation resembling hidradenitis suppurativa (Figures 1 and 2). Subungual hyperkeratosis and onycholysis were seen in some fingernails (Figure 3). Examination of the cardiovascular and respiratory systems was normal. The liver and spleen were not palpable and there was no lymphadenopathy.

Laboratory tests which included complete blood count, fasting blood sugar, creatinine, and electrolytes were within normal limits. Urinalysis showed a specific gravity of 1.000. The liver function tests were mildly elevated and hyperlipidemia was detected. LH and FSH levels were below normal. Thyroid function test showed T_3 124 ng/dl (80-180), T_4 4.73 µg/dl (4.5-11), FT_4 0.52 µg/dl (0.9-19), TSH 3.2 mU/ml (0.23-4.0). Hormonal study showed growth hormone deficiency, hypogonadotrophic hypogona-dism, central hypothyroidism and central diabetes insipidus.

Chest X-ray showed osteolytic lesions at right acromial process. The MR study showed suprasellar mass involving the hypothalamus and optic chiasm. Pus from the lesions at the axilla and groin were sent for Gram's staining, which showed a few gram-positive cocci. Pus sent for Wright's staining, acid fast and modified acid fast staining showed no organisms. Pus culture for bacteria showed a few *Staphylococcus aureus* and few diphtheroids. Pus cultures for mycobacteria and fungus were negative. KOH preparation and mycologic culture from the abnormal fingernails were negative.

He was diagnosed with LCH with multi-organ involvement due to the presence of diabetes insipidus and osteolytic lesions. The skin lesions at both axillae and groins were diagnosed as hidradenitis suppurativa. Initially he was treated with oral cloxacillin and wound care for his skin lesions. In spite of 3-week of oral antibiotics, the lesion did not show any improvement. Skin biopsies at the left axilla and left groin showed aggregation of large mononuclear cells with eccentric horse-shoe shaped

Figure 1.

Figure 2.

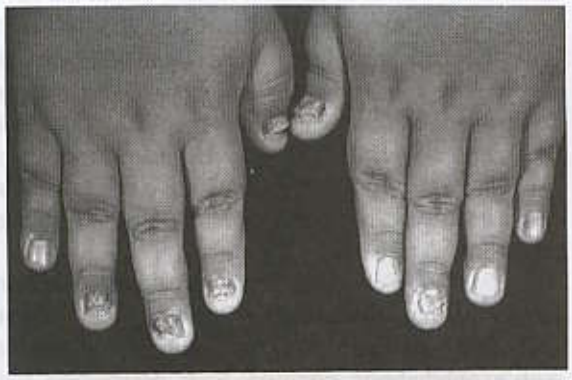
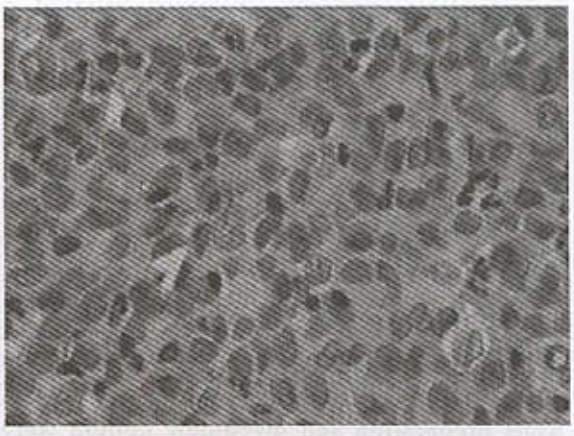


Figure 3.



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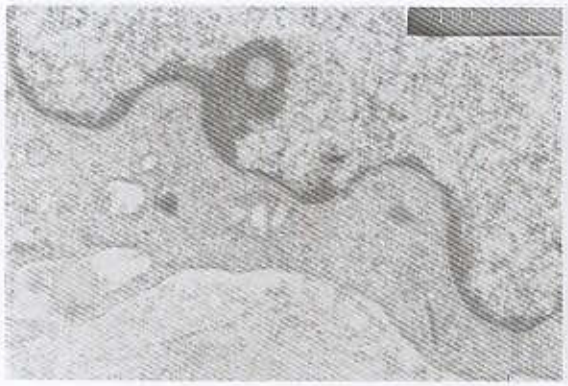

Figure 5.

nuclei and abundant eosinophilic cytoplasm infiltrating the reticular dermis (Figure 4). These large cells were positive for S100 protein and negative for macrophage marker (KP-1). Ultramicroscopic study of the skin lesion showed tubular structures of variable length with a striated central core identical to Birbeck granules (Figure 5). Some of them were dilatated at the end. The patient was treated with vasopressin nasal spray for diabetes insipidus, cranial radiation for pituitary involvement from LCH, eltroxin (0.1 mg/day) for hypothyroidism and simvastatin (10 mg/day) for hyperlipidemia. For his skin lesions, we started 60 mg per day of prednisolone for the first two weeks, which was tapered to 45 mg per day, 30 mg per day and 20 mg per day. The skin lesions resolved within 8 weeks. Since he also had subungual hyperkeratosis of some fingernails and clinically suspected onychomycosis, even though KOH preparation and mycologic culture were negative on two occasions, we started pulsed itraconazole therapy (400 mg per day for 7 days each month). He received 2 pulses of itraconazole treatment but his fingernails did not show any improvement.

DISCUSSION

Langerhans cell histiocytosis (LCH), formerly known as Histiocytosis X implies a group of diseases, which are characterized by abnormal proliferation and infiltration of Langerhans cells. This group of disorders can involve many organ systems, but primarily affect bone, skin, lymph node, lung, liver, spleen, endocrine gland and nervous system. The pathogenesis of LCH is still unclear. It has been classified as a neoplastic process, a reactive disorder or an aberrant immune response. Recently, Willman CL et al detected clonal histiocytes in the lesion of LCH which is suggestive of neoplastic disorder. This disorder possibly arises from somatic mutations that cause the clonal expansion of Langerhans cells.[8]

In 1987, The Histiocyte Society classified the histiocytosis into 3 classes; Class I : Langerhans cell histiocytosis, Class II : histiocytoses of mononuclear phagocytes other than Langerhans cells, and Class III : malignant histiocytic disorders.[9] In 1997 The Histiocyte Society offered a reclassification; Class I : dendritic cell related disorders, Langerhans cell histiocytosis, Class II : macrophage-related disorders, hemophagocytic syndrome, and Class III Malignant disorders.[10] Clinically, LCH had been divided into clinical entities, i.e. Letterer-Siwe disease (LSD), Hand-SchUller-Christian disease (HSC), and eosinophilic granuloma (EG).

Letterer-Siwe disease is an acute and disseminated form of LCH. It begins within the first 6 months of life in one-third of cases and before 2 years of age in most of the others. Organ involvement may include skin, bone, bone marrow, spleen, lymph node, liver and lung. Cutaneous manifesta-tions are very common in LSD. The typical lesions are multiple yellowish erythematous papules covered by scales or crusts located on the trunk and scalp resembling seborrheic dermatitis.

Hand-SchUller-Christian disease has a better prognosis than Letterer-Siwe disease. It was first described by Hand in 1893. He reported a patient with exophthalmos, polyuria, bony destruction and multiple organ involvement, believed at that time to be a form of tuberculosis. Similar clinical cases were reported by SchUller and Christian in 1915 and 1920 respectively. HSC is originally considered to embrace the triad of exophthalmos, diabetes insipidus and osteolytic bone lesions, but the triad manifestations may not be seen together. Cutaneous involvement occurs in 35-65% of cases. Most of the skin lesions are erythematous and crusted papules which

resemble seborrheic dermatitis. They particularly affect the scalp, anterior chest wall, axillae and buttocks. Other skin findings that have been previously reported include xanthomatous eruption, petechiae, and ulcers.

Eosinophilic granuloma is a localized, benign form of LCH that occurs mainly in adolescent boys and young adults. The granulomatous lesions often involve flat bones (skull, rib, vertebral column, pelvis) more than long bone (humerus, femur). Muco-cutaneous lesions are rare.

Endocrine involvement is one of the finding in LCH. Infiltration of the hypothalamic pituitary axis (HPA) has been reported in 5-50% of the autopsies of patients with LCH. Diabetes insipidus (DI) is the most common endocrine abnormality, reported in 15-50% of patients with LCH. Kaltsas et al[11], have evaluated the frequency and progression of LCH-related anterior pituitary in 12 adult patients with LCH and DI. Anterior pituitary hormonal deficiencies developed in 8 of 12 patients after follow up over the course of 20 years. GH deficiency developed in 8 patients, hypogonadotrophic hypogonadism in 7 patients, and TSH and ACTH deficiency in 5 patients. Five patients developed panhypopituitarism.[11]

DI with structural changes in the HPA often heralds the involvement of other parts of the brain with more global neuropsychological sequelae. The signs and symptoms of nonendocrine hypothalamic (NEH) involvement range from disturbances in social behavior, appetite, and temperature regulation, to abnormal sleeping patterns. Kaltsas et al also found NEH dysfunction in 7 of 8 patients with LCH and anterior pituitary hormone deficiency at a median of 10 years of follow-up (range 1-23 years): 5 morbid obesity, 5 short term memory deficits, 4 sleep disorders and 1 adipsia.

Tissue pathology is necessary to diagnose LCH. Presumptive diagnosis requires a characteristic histopathologic feature, which is an infiltration of uniform cells with horse-shoe shape nuclei and abundant pale eosinophilic cytoplasm. S-100 positive or peanut agglutinin positive cell makes a probable diagnosis. Definite diagnosis of LCH needs an ultramicroscopic study of the tissue, which shows Birbeck granules in the cytoplasm of Langerhans cell.[12]

Our patient had LCH with multisystemic involvement, including the endocrine system, bone and skin. The presenting skin lesions in this patient are uncommon. To our knowledge, only one patient with HSC and hidradenitis suppurativa-like lesions has been reported by Mahzoon S, et al in 1980. They reported a 20-year-old man with diabetes insipidus, diffuse goitre and skin lesions at the axillae and inguinal area resembling hidradenitis suppurativa. The chest X-ray showed interstitial infiltration. Histopathology of the thyroid gland and skin lesions showed histiocytic infiltration. Oral prednisolone therapy was started to treat the pulmonary involvement. His skin lesions were treated by surgical excision and secondary wound healing with a good result.[13] In our patient, the skin lesions completely healed within 8 weeks of starting systemic prednisolone therapy.

We believed that the nail changes in our patient were one of the manifestations of LCH since KOH preparation and mycologic culture from the abnormal fingernails did not show any evidence of fungal infection and the patient did not respond to pulsed itraconazole treatment. Nail involvement in HSC disease was described by Kahn in 1963. He reported a patient with diabetes insipidus, bony defects of the mastoid processes, otitis media, lung involvement and granulating paronychia with pus under the fingernails.[14] In 1984, Timpatanapong P, et al performed a retrospective study of nail involvement in patients with Histiocytosis X. These included 7 cases of Letterer-Siwe disease, 4 cases of Hand-SchUller-Christian disease, and 4 cases of eosinophilic granuloma. Three patients with Letterer-Siwe disease had nail involvement including nail dystrophy, onycholysis, subungual hyperkeratosis, paronychia, subungual pustules and subungual purpura. No nail involvement was found in the cases of HSC and EG. They mentioned that nail involvement seemed to be an unfavorable prognostic sign in Langerhans cell histiocytosis.[15] The first report of nail pathology in Histiocytosis X was in 1984 by Holzberg M. He reported subungual hyperkeratosis with paronychia in a 22-month-old patient with Histiocytosis X. A longitudinal biopsy performed on the fingernail showed a collection of Langerhans cells in the nail bed and nail fold.[16]

The treatment of LCH depends on the extent of visceral organ involvement. Isolated skin involvement may regress spontaneously especially in infants. When treatment is indicated for isolated skin lesion, topical steroid or nitrogen mustard may be effective. For endocrine involvement, none of the treatments currently available is able to alter the course of LCH or to prevent its progression. Radiotherapy may be useful in achieving local control of tumor, but established anterior, posterior pituitary and other NEH dysfunctions do not improve in response to current treatment protocols. As the progression from DI to anterior pituitary hormone dysfunction may be greatly delayed, such patients with LCH and DI should undergo regular and prolonged endocrine assessment to establish anterior pituitary hormone deficiency and provide hormonal replacement. Chemotherapy should be considered for multiorgan involvement.

In conclusion, hidradenitis suppurativa-like lesions and nail changes are rare manifestation in LCH. We report a case of LCH with multiorgan involvement presenting with chronic recurrent ulcers at the axillae and groins. The skin lesions responded well to oral prednisolone. Diabetes insipidus and hypothyroidism were controlled by hormonal replacement.

Comment of the Head of Dermatology Department

This case illustrates that the Langerhans cell histiocytosis can have progressive course and needs the suppressive therapy. The understanding of the disease's natural course is crucial since it is not cured with drug. Patient counselling and closed follow up will help the patient from his suffering. In this case, the cutaneous and nail abnormalities are rare manifestations of LCH. The common infectious diseases of the skin and nail should be ruled out before the diagnosis of LCH is made.

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REFERENCES

1. Munn S, Chu AC. Langerhans cell histiocytosis of the skin. Hematol Oncol Clin North Am 1998; **12:** 269-86.
2. Srivuthana S, Shuangshoti S, Chomdej S, et al. Histiocytosis X : Hand-SchUller-Christian disease. J Med Assoc Thai 1980; **63:** 582-90.
3. Heyduk JW. Hand-SchUller-Christian disease. Oral Surg Oral Med Oral Path 1967; **23:** 29-35.
4. Dolezal JF, Thomson ST. Hand-SchUller-Christian disease in a Septuagenarian. Arch Dermatol 1978; **114:** 85-87.
5. Rodriguez-Valdes J, Cordoba M, Perez-Espinosa J. Hand- SchUller-Christian disease A case report. Cutis 1982; **29:** 256-58.
6. Zachary CB, Macdonald DM. Hand- SchUller-Christian disease with secondary cutaneous involvement. Clin Exp Dermatol 1983; **8:** 177-83.
7. Kaufman A, Bukberg PR, Werlin S, Young IS. Multifocal eosinophilic granuloma ("Hand- SchUller-Christian disease"). Report illustrating H-S-C chronicity and diagnostic challenge. Am J Med 1976; **60:** 541-48.
8. Willman CL, McClain KL. An update on clonality, cytokines and viral etiology in Langerhans cell histiocytosis. Hematol Oncol Clin North Am 1998; **12:** 407-16.
9. Writing Group of the Histiocyte Society. Histiocytosis syndrome in children. Lancet 1987; **1:** 208-9.
10. Favara BE, Feller AC, Pauli M, et al. Contemporary classification of histiocytic disorders. The WHO committee on histiocytic/reticulum cell proliferations. Reclassification. Med Pediatr Oncol 1997; **29:** 157-66.
11. Kaltsas GA, Powles TB, Evanson J, et al. Hypothalamo-pituitary abnormalities in adult patients with Langerhans cell histiocytosis: clinical, endocrinological and radiological features and response to treatment. J Clin Endocrinol Metab 2000; **85:** 1370-76.
12. Proietto G, Amatetti M, Amerio P, et al. Langerhans cell histiocytosis associated with diabetes insipidus: magnetic resonance imaging. Int J Dermatol 1996; **35:** 730-32.
13. Mahzoon S, Gray W. Multifocal eosinophilic granuloma with skin ulceration Histiocytosis X of the Hand-SchUller-Christian type. Arch Dermatol 1980; **116:** 218-20.
14. Kahn G. Nail involvement in histiocytosis-X. Arch Dermatol 1969; **100:** 699-701.
15. Timpatanapong P, Hathirat P, Isarangkura P. Nail involvement in Histiocytosis X A 12-year retrospective study. Arch Dermatol 1984; **120:** 1053-56.
16. Holzberg M, Wade TR, Buchanan ID, et al. Nail pathology in histiocytosis X. J Am Acad Dermatol 1985; **13:** 522-24.