

A Case Report : A 7-Year-Old Boy with Hand-Schüller-Christian Disease

Narong Tungpakorn, MD

Department of Ophthalmology, Sawanpracharak Hospital, Nakhonsawan

การตรวจหาสาเหตุของภาวะตาโปน (exophthalmos) ในเด็ก อาจทำได้ยาก โดยเฉพาะหากมีอาการแสดงของระบบอื่น ๆ ของร่างกายร่วมด้วย จักษุแพทย์ควรรู้จักอาการและอาการแสดงของโรคต่าง ๆ ที่เกี่ยวข้องกับตา เช่น Hand-Schüller-Christian เพื่อให้สามารถให้การวินิจฉัยโรคได้อย่างถูกต้อง

Purpose : To present a case of classical triads in a patient with Hand-Schüller-Christian disease.

Methods : Case report.

Results : A 7-year-old boy presented with bilaterally slow progressive exophthalmos and subcutaneous nodules in the scalp and chin for 2 years. Radiologically, the skeletal survey revealed irregular well defined osteolytic area with thin, sclerotic borders limited to skull vault. On enquiry, he also gave symptoms of diabetes insipidus. Tissue biopsy and immunostainings have had Langerhans cell histiocytosis and positives for CD1a, S100 and CD68. The patient was diagnosed closely to Hand-Schüller-Christian disease. Management of Hand-Schüller-Christian disease includes open biopsy for diagnosis, surgical curettage, localized radiotherapy, chemotherapy in acute and maintenance phase, supportive therapy and surgery in specific indications. Long-term monitor should be considered and consulted for associated abnormalities.

Conclusions : Hand-Schüller-Christian disease is a rare entity comprising of exophthalmos, diabetes insipidus and geographical map skull. Though the triads remain important for diagnosis, number of other features have also been described. Long term surveillance should be emphasize to prevent loss of function and risk monitoring.

Key words : Hand-Schüller-Christian disease, Histiocytosis, Langerhans cell histiocytosis, exophthalmos, diabetes insipidus

Correspondence to : Tungpakorn N, Department of Ophthalmology, Sawanpracharak Hospital, A.Muang, Nakhonsawan 60000, Thailand. Phone : 0-5621-9888, Fax : 0-5621-9899, E-mail : mootpk@yahoo.com

Introduction

Histiocytosis is a broad term encompassing different clinico-anatomic pattern. It was first described in medical literature around the turn of the 20th century¹. It is a group of enigmatic disorders, the etiology and pathogenesis of which still remained unknown.

Hand-Schüller-Christian disease is a rare disease of Langerhans cell histiocytosis in which lipid accumulate in the body and manifest as histiocytic granuloma in bone, particularly in skull; the skin; and viscera, often with hepatosplenomegaly and lymphadenopathy. Exophthalmos and diabetes insipidus may be present. Both sexes affected, with a slight male predominance. The disease is seen in children and young adults, seldom in elderly persons. Onset usually occur before the age of six years. It's clinical course in unpredictable. As originally described, this syndrome included the classic triad of unilateral or bilateral exophthalmos, diabetes insipidus and defect in the membranous bones of the skull. Clinical features may also include defects in the mandible, long bones, pelvis, ribs, and spine.

This report is to present a patient with Hand-Schüller-Christian disease with typical classical triads.

Case Report

This patient was a young boy with 7 years old and was domiciled in San-kha-buri, Chainat. He was referred to the hospital because of his historical record showing that he has unusual tissues at both head and chin for approximately

2 years. He had several treatments, but all still be appeared. Recently the tissues had grew up for 2 weeks, especially the left side of his chin.

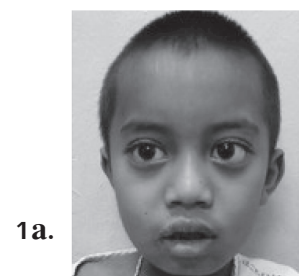
In addition, his eyes have had bilateral slow progressive exophthalmos for 2 years. His eyes had no blurred visions, no redness and painless.

A year prior to admission, he had a swollen tissue at the right side of his chin, but no fever. He received treatments and surgery here and was recommended for further treatments in Bangkok. Because of financial difficulties, he denied further treatments as well as the swollen tissue become smaller after the surgery.

On enquiry, he also gave history of fever off and on, polyuria and polydipsia for 2 years.

No history of accident, no family member has the same symptoms and no cancer reported in his family.

On physical examination, the patient has poorly built (Figure 1a, 1b and 1c), his temperature, pulse, respiration and blood pressure were within normal limits.





1c.

Figure 1a, 1b, and 1c. The pictures of a patient with poorly built.

In addition, the examination showed that the patient has multiple, soft, subcutaneous, mild tender nodules in the scalp. But the tissues at the left side of his chin was fixed with mandible bone (Figure 2) and found discrete, non-tender multiple cervical nodes, inguinal nodes and a small one on left axillary node.



Figure 2 The subcutaneous nodule at left side of submandibular area.

Based on abdominal examination, the patient has a slightly big abdomen, mild hepatomegaly, no splenomegaly and no abnormal mass.

At the time of the initial ophthalmic examination, the visual acuity was 20/20 in the both eyes. The patient's eyes were of equal size and exophthalmos (with axial type) (Figure 3).

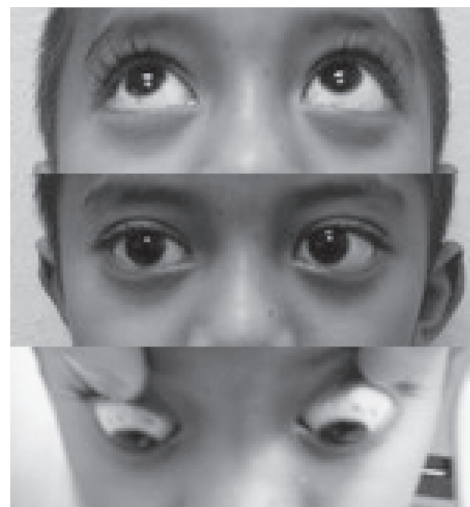


Figure 3 Bilateral exophthalmos.

Slit-lamp examination and fundus examination of the both eyes were revealed not abnormal (Figure 4).

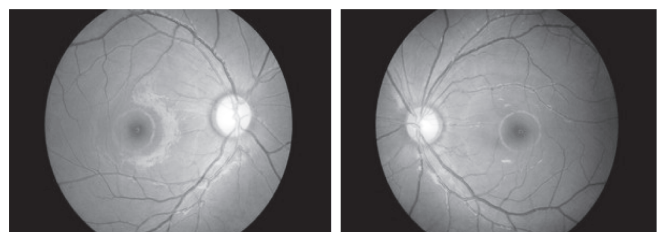


Figure 4 The funduscopy showed normal appearance.

Following investigations were carried out : Hemoglobin was 11.2 gms%, total WBC count was 9,400 cells/mm² with polymorphs 66% and

lymphocytes 34%, erythrocyte sedimentation rate was 89 mm/hr (Westergren), blood urea nitrogen, blood sugar and serum electrolytes were within normal limits.

Urine specific gravity was low (1.002) and daily urine output was about 2–3 litres. Stool examination was normal.

Radiologically, the chest x-ray film showed unremarkable. The skeletal survey revealed irregular well defined osteolytic area with thin, sclerotic borders limited to skull vault (Figure 5a. 5b.).

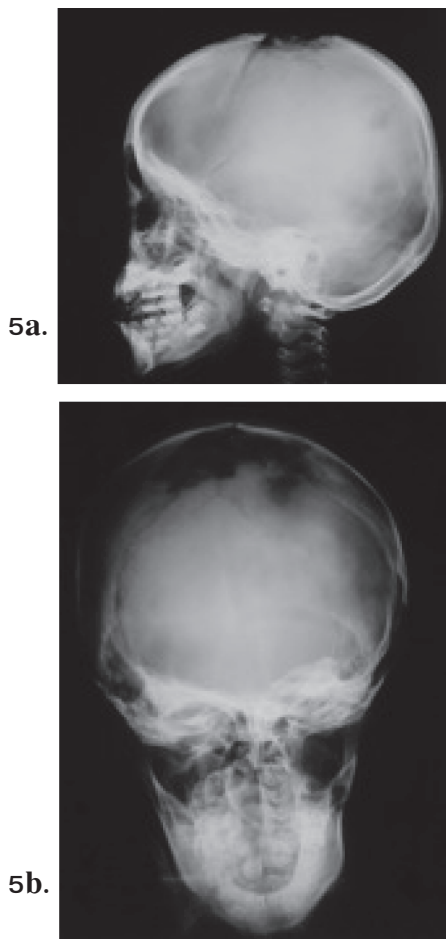


Figure 5a. and 5b. The skull films showed osteolytic lesions.

The cranial CT scan showed a spot representing bony destruction with adjacent enhancing soft tissue at both parietal region with no evidence of parenchymal lesion and slightly exophthalmos but not found retrobulbar mass. However, thick fluid or soft tissue density at right maxillary sinus is noted (Figure 6a. 6b. and 6c.).



Figure 6a. 6b. and 6c. The CT scan showed.

The examination of additional tissue biopsy: biopsy of the scalp swelling showed extensive fibrosis with hemosiderin deposition and the examination of tissue biopsy at left submandibular nodule mass found acute and chronic inflammation with granulation tissue, no malignancy is seen.

The result of cervical lymph nodes biopsy revealed nonspecific changes except the right submandibular lymph node that made langerhans cell histiocytosis and tumor cells are positive for CD1a, S100 and CD68 which was confirmed from special immunostaining from the faculty of Medicines, Chiang Mai University (Figure 7a. 7b. and 7c.).

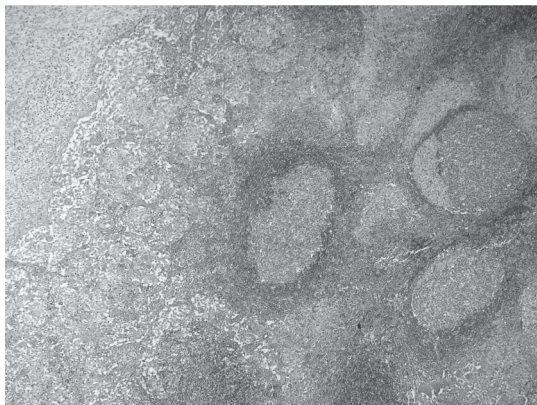


Figure 7a. Cell groups in sinuses and paracortex. (H&E)

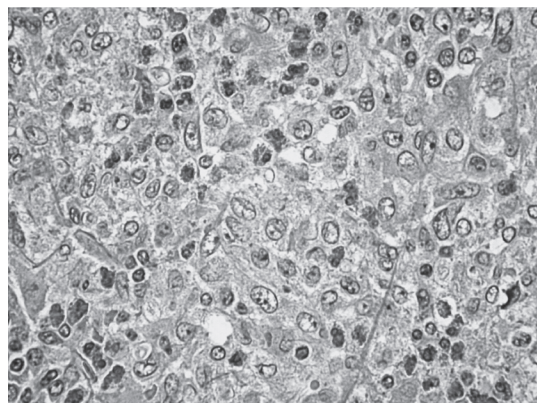


Figure 7b. Histiocyte-like cells with nuclear grooves. (H&E)

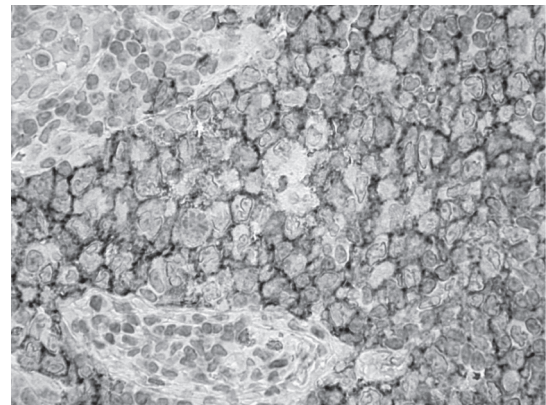


Figure 7c. Positive for CD1a immunostaining.

This patient was additionally examined for bone marrow biopsy and the result was negative for Langerhans cell infiltration and malignancy and the result from special immunostaining the CD1a staining shows negative result and the CD68 staining is positive for non-neoplastic cells.

Other associations, his audiogram result was mild slightly sensorineural hearing loss on left side.

Based on above mentioned physical examination and special examination as well as additional tissue examination of this patient, he was Hand-Schüller-Christian disease because of following classical triad :

- Lytic bone lesions especially skull defect.
- Central diabetes insipidus.
- Exophthalmos

There are several treatments for the disease in this group, including surgery (surgical curettage) which is suitable for patients with bone defect, localized radiotherapy or chemotherapy. All of these have same objective in providing treatments with minimal toxicity and no known risk to late effects.

This patient was treated with chemotherapy under control by pediatric hematologist according to the chemotherapeutic programme I of Mount Sinai School of Medicine¹ include Vinblastine at 0.15 mg/kg intravenously as single dose with Prednisolone at 2 mg/kg/day.

Moreover, if the treatment fails, the patient will be admitted to central hospital which have sophisticated equipment and specialists.

Discussion

Histiocytosis (histiocytic syndromes, reticuloses, reticuloendotheliosis) is an disease group rarely found in children. It includes various diseases concurrently found or as a result of the increasing number of cells histiocytes or macrophages (mononuclear phagocyte system, MPS) of bone marrow that widely spread into several tissues and resulted in clinical symptoms.

Histiocytosis is one of the diseases with ambiguity in terms of the disease name and classification. In the past, classification was made by using primarily the morphology of cells. However, the cells can have morphological transformation in many forms². The current standardized classification is the classification based on Histiocyte Society (1987). There are 3 classes

according to pathologic classification (Table 1).

1. Class I Histiocytoses (Dendritic cell histiocytosis)
2. Class II Histiocytoses (Ordinary histiocytosis, Non-Langerhans cell histiocytosis)
3. Class III Histiocytoses (Malignant histiocytosis syndromes)

Langerhans cell histiocytosis (LCH) is the most important disease in class I. There are abnormally incremental langerhans cells (LC) that group into granulomatous lesion in many organs. They may be localized or many locations concurrently or continuously⁴. It was mostly found in bone, approximately 80% of patients were found with lytic bone lesions frequently at skull. About 60% was found at skin. It was found in forms of seborrheic dermatitis, petechiae or purpura.

Approximately 30% of patients have hepatomegaly, splenomegaly, lymphadenopathy and may have liver dysfunction. This results in the increasing level of serum bilirubin and liver enzymes or swollen symptom and fluids in abdomen (ascites).

One of three patients may has diseases in bone marrow. The patient may look pale (anemia), neutropenia or thrombocytopenia.

Table 1 Classification of Histiocytosis Syndromes^{1,2,3}

1. Class I Histiocytoses (Dendritic cell histiocytosis)

1.1 Langerhans cell histiocytosis (LCH)

- Histiocytosis X
- Eosinophilic granuloma
- Letterer-Siwe disease
- Hand-Schüller-Christian disease
- Hashimoto-Pritzker syndrome
- Self-healing reticulohistiocytosis
- Reticulohistiocytoma
- “Pure” cutaneous histiocytosis-X
- Langerhans cell granulomatosis
- Type II histiocytosis
- Nonlipid reticuloendotheliosis

1.2 Interdigitating cell histiocytosis

1.3 Nonspecific dendritic cell histiocytosis

1.4 Dermatopathic lymphadenopathy

2. Class II Histiocytoses (Ordinary histiocytosis, Non-Langerhans cell histiocytosis)

2.1 Hemophagocytic syndromes

- Hemophagocytic lymphohistiocytosis (familial)
- Infection-associated hemophagocytic syndrome

2.2 Sinus histiocytosis with massive lymphadenopathy (SHML, Rosai-Dorfman disease)

2.3 Skin-based histiocytoses

- Juvenile xanthogranuloma
- Xanthoma disseminatum
- Papular xanthoma
- Benign cephalic histiocytosis
- Generalized eruptive histiocytoma
- Multicentric reticulohistiocytosis
- Progressive nodular histiocytosis

3. Class III Histiocytoses (Malignant histiocytosis syndromes)

Leukemias

- Acute monocytic leukemia (M5a, M5b)
- Acute myelomonocytic leukemia (M4)
- Juvenile chronic myelogenous leukemia
- Chronic myelomonocytic leukemia

Malignant histiocytoses

a. Ordinary histiocytic type

b. Dendritic cell type

: Langerhans’cell type

: Interdigitating cell type

: Nonspecific dendritic cell type

True histiocytic “lymphoma”

a. Ordinary histiocytic type

b. Dendritic cell type

: Langerhans cell type

: Interdigitating cell type

: Nonspecific dendritic cell type

About 25% have pulmonary dysfunction, resulting in asthma or abnormally fast breathing.

Approximately 15–20% have symptoms of diabetes insipidus which is polydipsia and polyuria.

Or may have other symptoms associated with central nerve system.

From above, there are many different symptoms and clinical locations of this disease. This results in some patients have localized symptoms, for example, at bone. Some have few symptoms and disappear and classified as Eosinophilic granuloma.

Some patients having bone disease with exophthalmos and diabetes insipidus are diagnosed as having Hand–Schüller–Christian disease.

And babies having fever, hepatosplenomegaly, lymphadenopathy as well as skin lesions with severe symptoms was diagnosed as having Letterer–Siwe disease⁵.

The incidence of LCH is 1 in 2 million and a male predominance has been observed with a male to female ratio of 3:2⁶. Mostly have 2–3 years old⁷ but may affect any age^{8,9}.

Currently it is believed that LCH was caused by Langerhans cells that response to the stimulation by foreign antigens or repeated virus infection. This results in Langerhans cells increase significantly and uncontrollably and ultimately causes several symptoms of this disease.

There are some clinical characteristics that have some impact on diagnosis¹⁰ including:

- The age of the patient
- Extent of the disease

– The degree of dysfunction of specific organs particularly, the hepatic, pulmonary and hematopoietic systems.

Since LCH is not a cancer under the current concept, the treatment does not need a complete remission like the cancer treatment. Only adequate treatments to control the disease and make patients alive are necessary in providing treatments with minimal toxicity and no known risk to late effect. They may be treated by surgical curettage, localized radiotherapy and chemotherapy or bone marrow transplantation in some cases.

Conclusion

Hand–Schüller–Christian disease is a rare entity comprising of exophthalmos, diabetes insipidus and geographical map skull¹¹. The management of this disease is on following principle, i.e. open biopsy for diagnosis, curettage, chemotherapy in acute and maintenance phase, supportive therapy, control of diabetes insipidus and surgery in specific indications. Long term surveillance should be emphasize to prevent loss of function and malignant monitoring.

Acknowledgement

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รายงานผู้ป่วย : เด็กชายไทยอายุ 7 ปี ที่มาด้วยกลุ่มอาการโรค Hand-Schüller-Christian

นายแพทย์ณรงค์ ตั้งภากรณ์
กลุ่มงานจักษุวิทยา โรงพยาบาลสวรรค์ประชารักษ์ นครสวรรค์

วัตถุประสงค์ : เพื่อนำเสนอผู้ป่วยกลุ่มอาการโรค Hand-Schüller-Christian ที่มาด้วยลักษณะอาการสำคัญ 3 อย่าง

วิธีการศึกษา : รายงานผู้ป่วย (case report)

ผลการศึกษา : ผู้ป่วยเด็กเพศชาย อายุ 7 ปี มีอาการตาโปน (exophthalmos) ค่อยๆ โปนมากขึ้นเป็นเวลา 2 ปี ร่วมกับมีก้อนเรื้อรังที่บริเวณศีรษะและคาง โดยตรวจภาพถ่ายรังสีพบลักษณะกระดูกแห่งที่ขอบเรียบ (punched-out) และพบอาการของเบาจืด (diabetes insipidus) ประกอบกับผลการตรวจชิ้นเนื้อ รวมทั้งการย้อมพิเศษทางอิมมูโน (immuno-staining) ให้ผลเป็น Langerhans cell histiocytosis และให้ผลบวกต่อ CD1a, S100 และ CD68 จากการย้อมพิเศษ ดังนั้นจึงให้การวินิจฉัยเป็น กลุ่มอาการโรค Hand-Schüller-Christian ซึ่งแนวทางในการรักษาในปัจจุบัน อาจแค่ผ่าตัดเฉพาะที่ (surgical curettage), การฉายแสงเฉพาะที่ (localized radiotherapy), หรือการใช้ยาเคมีบำบัด (chemotherapy) นั้นขึ้นกับว่าผู้ป่วยมีรอยโรคที่ใด และมีปัจจัยเสี่ยงมากน้อยแค่ไหน โดยในผู้ป่วยรายนี้ได้รับการรักษาโดยวิธียาเคมีบำบัด และต้องคอยเฝ้าสังเกตภาวะแทรกซ้อนที่อาจเกิดตามมา รวมทั้งการให้คำปรึกษาแก่ครอบครัว ประกอบกับควรปรึกษาแพทย์เฉพาะทางระบบอื่นๆ ร่วมด้วย เพื่อการรักษาที่เหมาะสมกับผู้ป่วย

สรุป : กลุ่มอาการโรค Hand-Schüller-Christian เป็นกลุ่มอาการที่พบได้ค่อนข้างน้อย มีอาการตาโปน ภาวะเบาจืด ร่วมกับตรวจพบรอยแห่งของกระดูกกะโหลก ซึ่งมีแนวทางในการรักษาหลายวิธีร่วมกัน เพื่อให้ผลของการรักษาผู้ป่วยดียิ่งขึ้น รวมทั้งจำเป็นต้องติดตามผลการรักษาต่อเนื่องแก่ผู้ป่วย

คำสำคัญ : กลุ่มอาการโรค Hand-Schüller-Christian, Histiocytosis, Langerhans cell histiocytosis, ภาวะตาโปน, ภาวะเบาจืด