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

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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

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Introduction

Histiocytosis is a broad term encompassing different clinic–anatomic pattern. It was first described in medical literature around the turn of the 20th century. 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.

![1a](image1)

![1b](image2)
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 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.

**Figure 3** Bilateral exophthalmos.

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

**Figure 4** The fundoscopy 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.).

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

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 Medicine\(^1\) 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 forms\(^2\). 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 continuously\(^4\). 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. **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 reticuloendotheliosis
      - 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 reticuloendotheliosis
      - 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 disease.

The incidence of LCH is 1 in 2 million and a male predominance has been observed with a male to female ratio of 3:2. Mostly have 2–3 years old but may affect any age.

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 diagnosis including:

- The age of the patient
- Extent of the disease
- The degree of dysfunction of specific organs particularly, the hepatic, pulmonary and hematopoetic 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 skull. 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.

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References


รายงานผู้ป่วย: เด็กชายไทยอายุ 7 ปี ที่มาด้วยกลุ่มอาการโรค Hand-Schüller-Christian

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วัตถุประสงค์: เพื่อนำเสนอผู้ป่วยกลุ่มอาการโรค Hand-Schüller-Christian ที่มีอาการลักษณะอาการสำคัญ

วีวิศึกษา: รายงานผู้ป่วย (case report)

ผลการศึกษา: ผู้ป่วยเด็กเพศชายอายุ 7 ปี มีอาการตาโตไป (exophthalmos) ที่เยี่ยมๆ ไปมากขึ้นเป็นเวลา

2 ปี รวมถึงมีอาการร่างกายต่างๆ เช่น ความตื่นเต้น แข็งแรง ปวดตัว ที่ด้านขวาของพร้อมที่สุด (punched-out) และพบอาการของเบาะ (diabetes insipidus) ที่ต้องการการตรวจด้วยเครื่องมือที่มีประสิทธิภาพ (immuno-staining) ให้

ผลเป็น Langerhans cell histiocytosis และให้ผลบวกต่อ CD1a, S100 และ CD68 จากการย้อมพีคิท ดังนั้นจึงได้รับการวินิจฉัยเป็นกลุ่มอาการโรค Hand-Schüller-Christian ซึ่ง

แนวทางในการรักษาในปัจจุบัน อาจแก้ไขด้วยการรักษาแบบเชื้อภาพ (surgical curettage), การรักษาแบบเลือดการรักษา (localized radiotherapy), หรือการใช้ยาเชื้อภาพ (chemotherapy) นั้น

กับอาการผู้ป่วยรายนี้ ที่มีอาการที่น่าจะเป็นผลของอาการแนวที่มีภาวะโรคหลอกหลังจากที่อาการมีการเปลี่ยนแปลงตามความ

ที่การให้คำปรึกษาผู้ป่วยรายนี้ ประพฤติเป็นسكر์รักษาแพทย์เฉพาะทางระบบอื่นๆ ร่วมด้วย เพื่อการรักษาที่เหมาะสมกับผู้ป่วย

สรุป: กลุ่มอาการโรค Hand-Schüller-Christian เป็นกลุ่มอาการที่พบได้ค่อนข้างน้อย มีอาการ

ตาโตไป ภาวะแทรกซ้อน รวมถึงตรวจพบการบริหารการรักษารักษาที่มีความเสี่ยง รวมทั้งเจาะเป็นต้องจดตาม

ผลการรักษาค่อนข้างแก้ปัญหา

คำสำคัญ: กลุ่มอาการโรค Hand-Schüller-Christian, Histiocytosis, Langerhans cell histiocytosis, ภาวะตาโตไป, ภาวะแทรกซ้อน