Case 28
A 30-year-old Thai man from Bangkok
Chief complaint: 1-year history of asymptomatic progressive mass on the scalp.

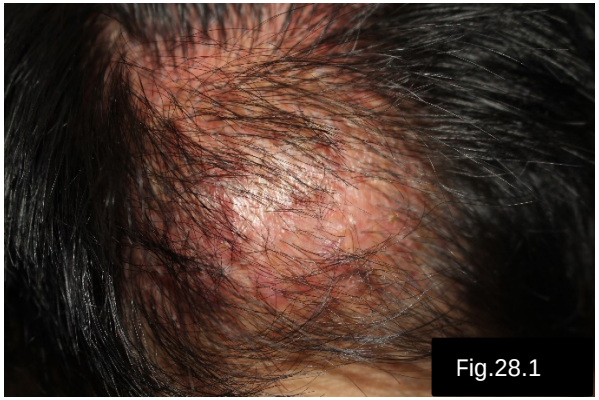
Fig.28.1

Present illness:

The patient was diagnosed with multi-system langerhans cell histiocytosis (LCH) since October 2012. At that time, he presented with recurrent pneumothorax and pituitary involvement (i.e., diabetes insipidus and growth hormone deficiency). Bronchoalveolar lavage cytology revealed increased Langerhans cells. He received chemotherapy, including vinblastine, etoposide, and prednisolone, as well as radiotherapy. The patient showed complete response.

One year earlier, he noted multiple palpable masses on his scalp. (Fig.28.1)The lesions gradually enlarged without pain or pruritus. He also complained of polyuria and polydipsia. He denied a history of significant weight loss, malaise, fever, bone pain or dyspnea.

Family history: There was no family history of similar lesions.

Physical examination:

- V/S: T 37.4 °C, P 90 bpm, RR 18 min, BP 130/80 mmHg
- HEENT: Not pale conjunctivae, anicteric sclerae
- Heart and lungs: Normal
- Lungs: normal breath sound, no adventitious sound
- Abdomen: No hepatosplenomegaly
- Lymph node: No lymphadenopathy

Dermatological examination:
Multiple huge, fixed, non-tender, smooth surface, soft-to-rubbery, erythematous masses with 5 cm in their largest diameter, on occipital and parietal scalp areas

Histopathology: (S19-008811, Scalp)

- Nodular cell infiltrate of large mononuclear cells with abundant eosinophilic cytoplasm and kidney-shaped nuclei admixed with lymphocytes, eosinophils, neutrophils and multinucleated giant cells (Fig.28.2-3)

Immunochemistry:

- Positive: S100 (Fig.28.4), CD1a (Fig28.5)
- Negative: CD68

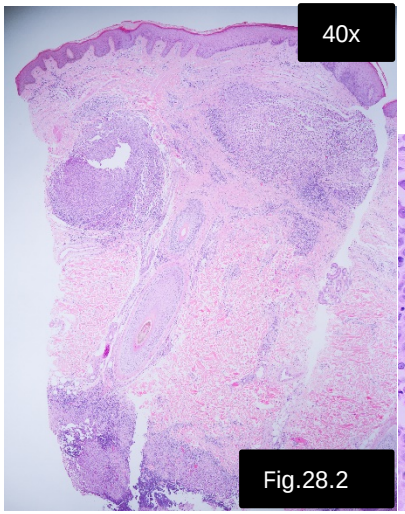

Fig.28.2

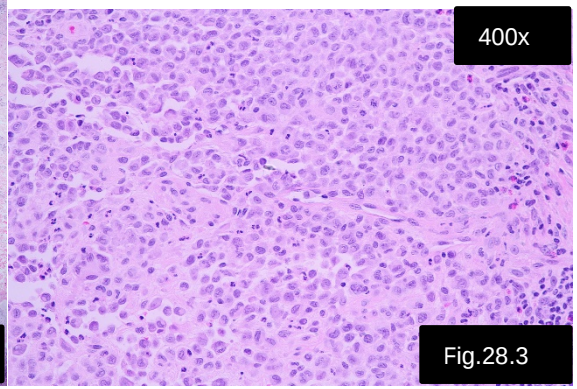

Fig.28.3

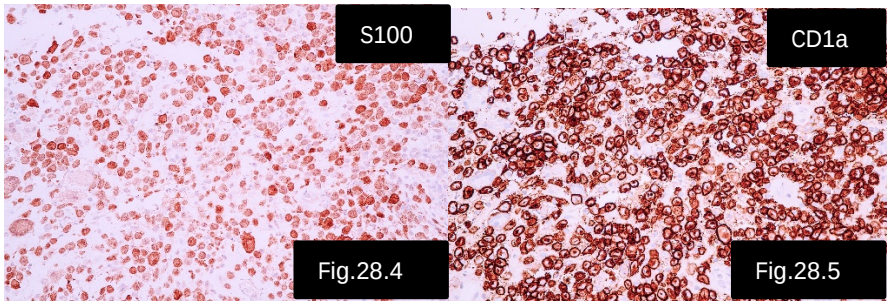

Fig.28.4 Fig.28.5

Laboratory investigations:

- CBC: Hb 15 g/dL, Hct 47%, Plt 413,000 /mm^3, WBC 8,330 /mm^3 (N 72%, L 20%, M 6%, E 2%)
- LDH: 317 U/L (240-480 U/L)
- Morning cortisol = 16.3 ug/dL (5-25 Ug/dL)
- Serum free T4 = 0.97 ng/dL (0.7-1.48)
- Prolactin = 18.7 ng/mL (3.4-19.4)
- Testosterone serum = 198 ng/dL (240-871)
- AST/ALT: 30/55 U/L
- BUN/Cr: 8/0.75 mg/dl
- MRI brain: pituitary appears normal, multiple enhancing lesions at occipital and posterior parietal regions
- CT chest: multiple cystic lesions both lungs, LN not enlarge, no pneumothorax
- CT abdomen: fatty liver, not involved, normal spleen size, LN negative
- Bone marrow biopsy: normocellular marrow with multilineage maturation, negative for LCH involvement

Diagnosis: Multi-system langerhans cell histiocytosis (lungs, skin)
Treatment:

Specific treatment

- Chemotherapy (vinblastine, prednisolone, methotrexate, leucovarin)
- Testosterone 150 mg intramuscular monthly
- Desmopressin acetate 0.025 ml intranasal twice daily

N.B. He remains hospitalized in another hospital for recurrent pneumothorax. He underwent medical pleurodesis and lobectomy. A follow-up CT chest is scheduled for re-evaluation of treatment.

Presenter: Pitchaya Jaruvijitrattana, MD
Consultant: Poonkiat Suchonwanit, MD
Discussion:

Langerhans cell histiocytosis (LCH), a rare non-inherited clonal proliferative disease of Langerhans cell, was first described in 1953.[1] The disease characteristic is that pathologic Langerhans cells accumulate in various organs including bone, skin, lymph node, hypothalamic-pituitary/central nervous system, lungs, hematopoietic system, liver, spleen, and less common thyroid and gastrointestinal tract.[1, 2]

Langerhans cell histiocytosis occurs most often in children age ranging from 1 to 4 years. The estimated incidence of LCH in adults is 1-2 cases per million. LCH has been found more often in males with a roughly male to female ratio of 2 to 1. [2-4]

The etiology and pathogenesis remains unclear. However, it is suggested that LCH might be a more neoplastic disease rather than reactive disorder. LCH is now defined as an inflammatory myeloid neoplasm in the revised 2016 Histiocyte Society classification. Approximately 60% of LCH-cells bear a *V600E* mutation in the *BRAF* oncogene.[5] Studies have reported that the presence of circulating cells carrying *BRAF V600E* mutations is associated with high-risk clinical status (multisystem disease and liver, bone marrow, spleen involvement) and with a two-fold increase in the risk of recurrence.[2, 6]

Association between adult LCH and solid tumor or hematologic malignancy has been reported. The common solid tumors are lung

and breast cancer. Interestingly, the largest percentage of other malignancies that was diagnosed before a LCH diagnosis is hematologic malignancy.[7] Adult LCH with cutaneous involvement shows an association with increased risk of a second hematologic malignancy, including myelodysplastic syndrome, acute myelomonocytic leukemia, diffuse large B-cell lymphoma, peripheral T-cell lymphoma, and histiocytic sarcoma[8]

The cutaneous manifestation of LCH is highly varied. The presentations are characterized by a seborrhea-like eruption, solitary or multiple papules, vesicles, varicella-like eruptions, pustules, crusted plaques, nodules, and purpuric nodules. Sites of involvement are scalp, nose, shoulder, chest, back, trunk, knee, skin folds, and oral cavity. Nail involvement can present as paronychia, nail fold destruction, onycholysis, subungual keratolysis, longitudinal grooving and pigmented and purpuric striae of the nail bed.[1, 2, 8]

Diagnosis is based on histologic and immunophenotypic examination. The proliferative pattern clinically presents with papules may reveal a proliferation of LCH cells in the papillary dermis admixed with eosinophils, neutrophils, lymphocytes, and plasma cells. Epidermal infiltration by Langerhans cells and secondary features such as crusting, pustule formation, hemorrhage or necrosis may be found.[1, 3, 9]

To confirm the diagnosis of LCH, positive immunostaining for CD1a, S100 and Langerin (CD207) or demonstration of Birbeck granules on electron microscopy may be required. In contrast, they show negative immunostaining for dermal dendrocyte markers (factor XIIIa) and macrophage/monocyte markers (CD68, CD163 or HAM56).[9]LCH is classified into two groups (Table 1).[10] The prognosis of patients with LCH varies according mainly to particular type of involved organs—the increases risk of disease-related mortality in cases with vital organ involvement.

The treatment of LCH depends on disease severity and organ involvement. Topical corticosteroid, tacrolimus, imiquimod, and phototherapy (NBUVB, PUVA) have been reported to be effective in mild single system skin involvement. For more extensive cutaneous disease, thalidomide may be effective. Systemic therapy is strongly recommended for multisystem (MS) LCH or single systemic with multifocal lesions or with special site lesions. No standard treatments have been well-established, but a combination of vinblastine and prednisolone therapy could serve as the optimal option. Cytarabine or 2-chlorodeoxyadenosine (2-CdA) might be preferred as the first-line treatment.[11] Retrospective analyses of short-course chemotherapy with methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin in aggressive adult LCH have shown its moderate efficacy.[12] Another recent treatment is targeted therapy. Imatinib has been reported to be effective in refractory MS-LCH cases. Other drugs include dabrafenib and vemurafenib, however they are both investigated in ongoing clinical trials.[4]

Mass lesions in hypothalamus and/or pituitary glands are often treated with vinblastine/prednisone or 2-CdA. Although, most reported cases have shown that symptoms of diabetes insipidus or hormone dysfunction could not be normalized, hormone replacement therapy is still required.[4]

Our patient was diagnosed with recurrent MS-LCH (cutaneous and lung). Systemic chemotherapy (vinblastine, prednisolone, methotrexate, leucovarin) and hormone replacement therapy were administered. He remains hospitalized in another hospital for recurrent pneumothorax. He underwent medical pleurodesis and lobectomy. A follow-up CT chest is scheduled for re-evaluation of treatment.

Table 1 Classification of Langerhans-Cell Histiocytosis

Classification of Langerhans-Cell Histiocytosis	
Single-system Disease	
Localized (single site)	-bone -skin -lymph node
Multiple sites	
Multi-system Disease	
Low-risk group	Low-risk organs (skin, bone, lymph node, pituitary)
High-risk group	high-risk organs (hematopoietic system, lungs, liver, and spleen)

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