Case 13

Eczema-like lesions on the neck and trunk

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Patient: A 63-year-old Thai man from Bangkok

Chief complaint: Rash on the neck, chest and abdomen for 2 months

Present illness:

Three months earlier, the patient noticed several painless and enlarging lumps on both sides of the neck. He also experienced fatigue, low-grade fever and unexplained weight loss.

Two months earlier, he developed an itchy rash starting on the abdomen and spreading to the neck and upper chest.

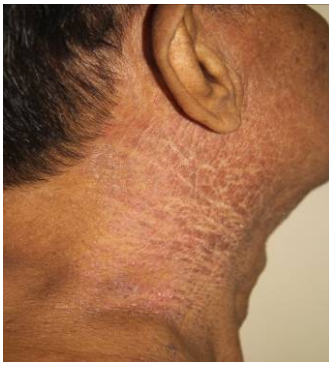
Past history:

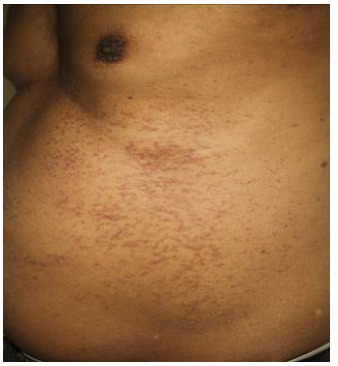
- Rheumatoid arthritis and chronic HBV infection for many years
- Newly diagnosed hypertension
- History of sulfonamide allergy
- 20-pack-year smoking history with 2 years of quitting

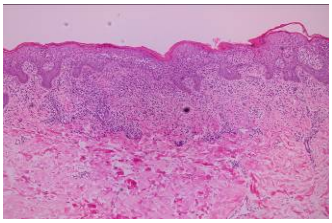
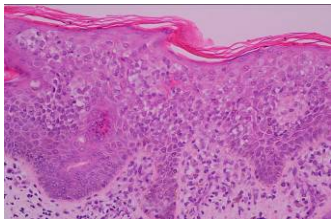
Current medications: Methotrexate 10 mg weekly, lamivudine 150 mg daily and hydrochlorothiazide 50 mg daily

Physical examination:

V/S: BT 37.5ºC, BP 130/80 mmHg, PR 108/min, RR 20/min
HEENT: No pale conjunctiva, no icteric sclera
Multiple, firm, non-tender bilateral cervical lymph nodes ranging from 0.5 to 1 cm in diameter
Solitary, firm, non-tender, mobile 3-cm mass in the right supraclavicular region
Heart and lungs: Unremarkable
Abdomen: No hepatosplenomegaly
Neurological system: Grossly intact





Skin examination:

- Multiple scaly erythematous patches with cracking on lateral aspects of the neck
- Multiple scaly erythematous papules, some of which coalesced to form plaques, located on the upper chest and abdomen

Histopathology:

Skin (S13-19325, abdomen)

- There is focal parakeratosis and epidermal hyperplasia in association with band-like infiltration of lymphocytes, a few eosinophils and a hint of Langerhans cells in the upper dermis and some exocytosis to the epidermis
- Immunostains: Positive for S-100 and CD1a

Lymph node (right cervical region)

- Marked sinusoidal and focal parenchymal infiltration by reactive histiocytes with phagocytic activity
- Immunostains:
  - Markedly increased atypical-looking histiocytes positive for CD68 and S-100, but negative for CD1a
  - Increased Langerhans cells positive for CD68, S-100 and CD1a
  - No CD34-positive blasts

Bone marrow

- Adequate cellular marrow showing active trilineage hematopoiesis
- No overt histologic and immunophenotypic evidence of involvement by Langerhans cell histiocytosis

Investigation:

Laboratory tests

CBC: Hct 34.7%, WBC 8260 (N69%, L19%, M12%), Plt 299,000/mm^3
Cr 0.97 mg/dL
LFT: ALP/GGT 287/564 UL, AST/ALT 22/64 U/L, TB/DB 0.8/0.5 mg/dL, TP/alb 73.5/29.5 g/L
LDH 131 U/L
ESR 77 mm/hr
Urinalysis: sp.gr. 1.030, pH 5.0, protein 1+, glucose/WBC/RBC negative

Imaging studies

Chest X-ray: Unremarkable

CT scan of chest and whole abdomen:

- Multiple tiny nodular opacities and small cysts scattered throughout both lungs, pulmonary Langerhans cell histiocytosis is possible
- Severeal supraclavicular, axillary, para-aortic, aortocaval, mediastinal and mesenteric nodes

- Few tiny non-enhancing hypodense lesions at segment VI/VII of right hepatic lobe

CT scan of the brain:

- Possible old lacunar infarction at left superior frontal gyrus
- Bones, soft tissue and orbits appear normal

Diagnosis: **Multisystem Langerhans cell histiocytosis**
(Lymph nodes, skin, liver and lung)
with risk-organ involvement

Treatment:

- 6-cycle induction chemotherapy with combination of vinblastine, etoposide and prednisolone
- Maintenance chemotherapy with the same protocol
- 0.1% Triamcinolone acetonide lotion to be applied to rash twice daily
- Mineral oil to be applied to dry skin as needed
- Hydroxyzine 10 mg orally every 8-12 hours as needed

Discussion:

Langerhans cell histiocytosis (LCH), previously called histiocytosis X, is a rare clonal proliferative disorder characterized by the accumulation of pathologic Langerhans cells (LCs) in a variety of organs. Historically, LCH was described under various names: Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma, and congenital self-healing reticulohistiocytosis (Hashimoto-Pritzker disease). In recent years, the term "Langerhan cell histiocytosis" has been recommended to be used instead, as it has been recognized that the disease exists as a spectrum ranging from self-healing to potentially lethal multisystem disease.

Despite its rarity, LCH is the most common among the histiocytic disorders.[1] LCH is far more common in children, especially those between the ages of 0 and 3, though it can occur at any age. The etiology remains not fully understood, and the nature of reactive or neoplastic process is still debated. Not only LCH cells showing a clonality, but also the discovery of *BRAF* point mutations in the majority of LCH lesions, indicates that it might be more a neoplastic disease than inflammatory disease.[1,2]

Although LCH can affect a wide range of organ systems, the most commonly involved sites appear to be bone, skin and pituitary gland. Less frequently, lymph nodes, liver, spleen, bone marrow and central nervous system (CNS) are also affected.[2,3] To stratify, LCH is clinically classified into (1) single-system LCH (SS-LCH) and (2) multisystem LCH (MS-LCH), which is further subclassified into involvement of low-risk organs (such as skin and lymph nodes) and high-risk organs (liver, spleen, bone marrow and CNS).[2] In fact, the lung was considered for many decades to be a risk organ, but the subsequent clinical data do not support this implication.[1]

While cutaneous manifestations are very common in LCH patients, isolated skin involvement appears to be somewhat infrequent, particularly in adults.[4,5] Cutaneous LCH is highly variable and can mimic many entities, including seborrheic dermatitis, eczema, psoriasis and intertrigo. Typical LCH lesion is a small rose-yellow papule or nodule, frequently showing thin scales and sometimes becoming crusted and ulcerated. Vesicles and pustules may concurrently occur, especially in neonate patients. Scalp and trunk are the

predilection sites for this type of LCH lesions.[1,2] Moreover, the presence of petechiae/purpura in the eruption is another characteristic feature, making an alert to the possibility of LCH.[4] In contrast, when LCH affects flexural and anogenital areas, it causes an erosion or ulceration.[2] Several clinical patterns of cutaneous LCH are recognized as follows: (1) a solitary papule/nodule, (2) multiple papules localized only on the scalp, (3) multiple/generalized papules, (4) ulcerations in skin folds/anogenital areas, and (5) a combination of generalized papules and ulcerations.[3,6] Besides, various changes of the nail are also observed in LCH patients, such as onycholysis, subungual hyperkeratosis and purpuric striae of the nail bed.[2] Among dermatological manifestations, the presence of petechiae/purpura or nail changes indicate a poor prognosis.[7]

The bone and pituitary gland are also commonly affected by LCH, usually presenting with osteolytic lesions and diabetes insipidus (DI) respectively. Lytic bone lesions can be single or multiple, and the skull, in particular temporoparietal region, is most often involved, typically showing "map lesions" on the radiograph.[2,7] Pulmonary LCH occurs more frequently in adults than children, displaying classic "honeycomb appearance" due to bulla formation or micronodular pattern on the imaging study.[7] In general, lymphadenopathy is not prominent in LCH; however, it seems to be more common in the fetal LCH cases. When lymph node is affected, the cervical region is the most common site. CNS involvement can result in tumor formation or neurodegeneration, but only tumorous CNS is considered as a risk organ.[2] Although involvement of the liver and spleen is not common, it is an unfavorable prognostic sign.[2,7] Bone marrow involvement rarely occurs, only found in the late phase of aggressive form of LCH. Systemic symptoms, such as fever, malaise and weight loss are frequently observed in aggressive cases.

The diagnosis of LCH is generally based on histological and immunophenotypic analysis of a lesional biopsy, requiring the finding of Birbeck granules by electron microscopy (EM) or CD1a/Langerin (CD207) positivity. Indeed, demonstrating Birbeck granules by EM is recognized as the gold standard for Langerhans cell identification.[1,2] Microscopic features of cutaneous LCH consist of a dense lichenoid infiltration of histiocytes, which have irregular vesiculated, often reniform nuclei and abundant cytoplasms, in the upper dermis with a strong epidermotrophism.[7]

In terms of treatment, the first step is to determine the number of organ systems involved, i.e. SS-LCH or MS-LCH. For SS-LCH involving the skin or bone, the management is usually nonaggressive. Limited skin lesions can be successfully treated with topical corticosteroids, topical nitrogen mustard and phototherapy (NBUVB or PUVA), whereas systemic therapies, such as thalidomide, azathioprine and methotrexate, are reserved for extensive cutaneous involvement or resistant cases. For MS-LCH patients, single-agent chemotherapy is recommended as the first-line treatment, 2-CDA (chlorodeoxyadenosine) for MS-LCH with risk-organ involvement and vincristin/prednisolone, etoposide or cytarabine for MS-LCH without risk-organ involvement. Combination chemotherapies are usually used for aggressive cases, and patients with MS-LCH involving bone marrow require bone marrow transplantation.[2]

Regarding the prognosis, it mainly depends on clinical features, the age at onset, the rate of disease progression and the number of organ systems involved. The onset at under the age of 2 years yields a poorer outcome, but this can be implied only when multiple system are involved.[1] Moreover, in case

of MS-LCH, another factor which can determine the prognosis of the disease is the patient's response to the treatment during 6-week of induction phase.[1] Furthermore, the association between LCH and secondary malignancies, including hematological and solid malignancies, has been described.[2,6] Thus, long-term follow-up in LCH patients is strongly suggested, not only for identifying disease recurrence and long-term complications, but also for recognizing the possible secondary malignancy.[1]

Our patient is a case of multisystem LCH involving skin, lung, lymph node and liver (which is a risk organ), presenting with generalized lymphadenopathy and eczema-like eruption on the common sites. LCH was diagnosed based on the histology and immunophenotype of skin and lymph node biopsy. As 2-CDA is not available, patient was treated with a combination of vinblastin and etoposide. However, the patient appeared to be not responsive well to the treatment. The disease progressed and the spleen, another risk organ, was also involved later on. The patient eventually died due to severe sepsis after 5 months of treatment.

References:

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