CASE REPORT

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Langerhans Cell Histiocytosis Presenting as Anterior Neck Mass in a Child: A Case Report*

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Abstract

Thyroid involvement in Langerhans Cell Histiocytosis (LCH) is rare. We report a 10-year-old Filipino male who presented with a rapidly enlarging goiter. Computed tomography scan showed thyroid and bilateral submandibular masses with malignant features, pulmonary blebs and hepatic cysts. Ultrasound-guided core needle biopsy findings were consistent with LCH and chemotherapy was initiated. This case demonstrates that LCH should be considered in patients with goiter. Multidisciplinary management is warranted to achieve proper diagnosis and institute timely treatment.

Key words: Langerhans Cell Histiocytosis, thyroid, multisystem LCH

INTRODUCTION

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by accumulation of pathologic Langerhans cells into organs.[1] These langerin-positive (CD207+) histiocytes may develop in any tissue, but a study of LCH organ involvement showed that the incidence is highest at the skeletal system at 80%, followed by the skin (60%), and lymph nodes (33%).[2] In children, LCH is usually a multisystemic disease, and involvement of the thyroid gland is extremely rare.[3]

CASE

A 10-year-old Filipino male consulted at the outpatient Pediatric Endocrinology clinic with a two-month history of a rapidly enlarging anterior neck mass. There was no dysphagia, hoarseness, cold or heat intolerance, or bowel movement changes. He had a height of 133 cm which was appropriate for age. Physical examination showed an anterior neck mass measuring 15 x 16 x 4 cm (L x H x W). Thyroid ultrasound showed thyroid gland with coarsened and nodular echopattern and enlargement of both submandibular glands. Thyroid function tests were normal with a FT3 of 2.45 pg/ml (reference range: 2-4.35), FT4 of 14.77 pg/ml (reference range: 7-18) and TSH of 3.63 uIU/ml (reference range: 0.25-4). After two weeks, the Otorhinolaryngology service performed fine needle aspiration biopsy. The fine needle aspiration cytology (FNAC) result was Bethesda system category IV: suspicious for follicular carcinoma and advised correlation with clinical and other radiographical findings. After one month, during which the patient had weight loss, poor appetite and dysphagia, he was admitted for possible thyroidectomy with neck dissection.

Family history revealed goiter on the maternal side. Past medical history revealed that three months prior to anterior neck enlargement, he had a history of recurrent bilateral spontaneous pneumothorax requiring video-assisted thoracoscopic surgery (VATS), blebectomy, and mechanical and chemical pleurodesis.

Hematology-oncology service and a pediatric airway team consisting of Critical Care, Pulmonology, Otorhinolaryngology, Anesthesiology, and Surgery co-managed the patient. Complete blood count showed anemia, leukocytosis with neutrophilic predominance, and thrombocytosis. Electrolytes and arterial blood gas were normal. Chest radiograph (Figure 1) revealed right pneumothorax. Urinalysis showed microscopic hematuria and pyuria. Repeat thyroid function tests showed normal FT3 of 4.2 pmol/L (reference range: 3.1-6.8), normal FT4 of 17.3 pmol/L (reference range: 12-22) and elevated TSH of 19.6 uIU/mL (reference range: 0.27-4.2). Computed tomography scan of the neck and chest (Figure 2) revealed thyroid mass

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with malignant features and local mass effect, invading the right internal jugular vein and superior vena cava. In addition, there were pulmonary blebs and multiple hepatic cysts that are not typical features of thyroid carcinoma.

Interventional radiology performed an ultrasound-guided core needle biopsy of the thyroid and lymph nodes, which showed atypical, medium-sized cells with abundant amphophilic to eosinophilic cytoplasm, centrally located, and grooved nuclei. These atypical cells are admixed with abundant eosinophils and showed strong immunoreactivity to CD1a, S100, and Langerin (Figure 3), which strongly supports a diagnosis of LCH. The previous cell block of his excised bleb was also reviewed and showed CD1a positivity, compatible with LCH. Bone marrow aspiration with biopsy and cranial CT scan showed normal results.

During admission, the patient initially received an anti-inflammatory dose of prednisone at 1 mg/kg/day, antibiotics for urinary tract infection, and levothyroxine at 2.1 mcg/kg/day for subclinical hypothyroidism. The patient developed pneumothorax prompting endotracheal intubation and chest tube thoracostomy. Upon stabilization, chemotherapy was initiated with the following treatment protocol: vinblastine 6 mg/m^2 once a week for 6 weeks and prednisone 40 mg/m^2 divided into 3 doses for 4 weeks. There was a significant decrease in goiter size within two weeks of chemotherapy. Three months after initiation of chemotherapy, thyroid function test showed normal FT3 of 4.89 pmol/L (reference range: 3.1-6.8), elevated FT4 of 22.35 pmol/L (reference range: 12-22) and TSH of 2.14 uIU/mL (reference range: 0.27-4.2). Levothyroxine was decreased to 1.7 mcg/kg/day. It was discontinued after a month in preparation for thyroid scan, which revealed normal sized, normofunctioning thyroid gland. Seven weeks after levothyroxine discontinuation, thyroid function test showed normal FT4 of 19.38 pmol/L (reference range: 12-22) and elevated TSH of 7.98 uIU/mL (reference range: 0.27-4.1). He denied cold intolerance, constipation, nor easy fatigability. Thus, the service opted to observe subclinical hypothyroidism.

The patient was noted to have polydipsia and polyuria with negative fluid balance. Central diabetes insipidus (DI) was considered, however, results of the water deprivation test was inconclusive with serum osmolality of 287.7 mOsm/kg and urine osmolality of 560 mOsm/kg. The test had to be terminated when the patient lost 5% of his weight. Hence, further monitoring was suggested. Cranial MRI was requested showing a normal pituitary bright spot (Figure 4). The patient was discharged and is currently on continuation phase of his chemotherapy.

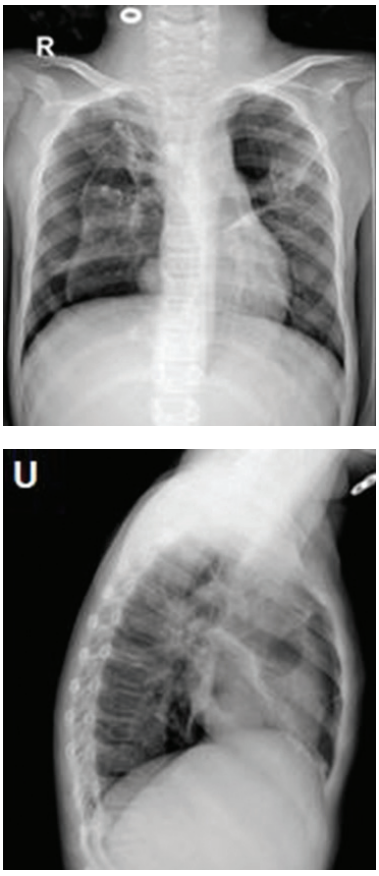

Figure 1. Chest radiograph showed pneumothorax on the right hemithorax, ovoid density on left upper lobe possibly bullous changes, and possible segmental atelectasis on the left hilum.

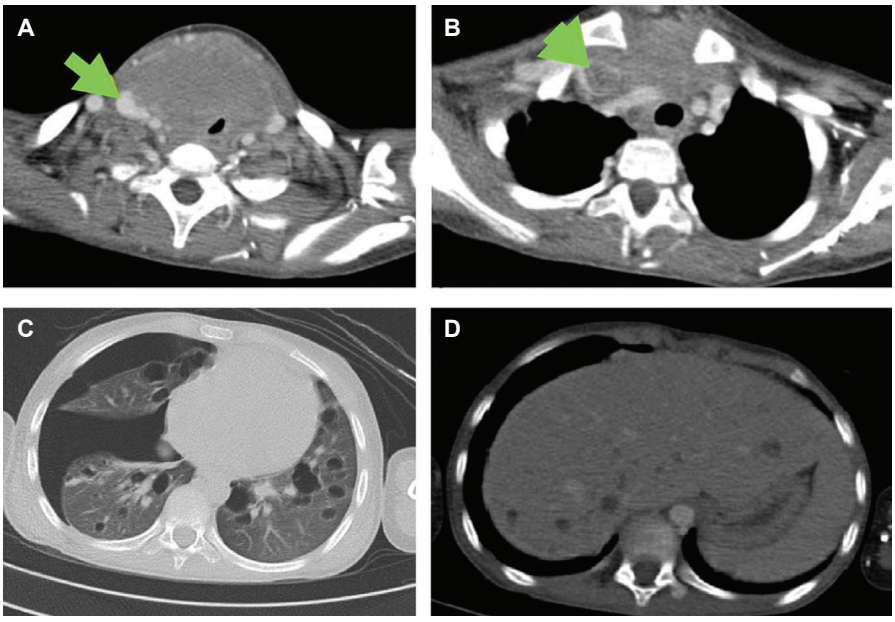

Figure 2. CT scan showing a heterogeneously large lesion replacing the normal looking thyroid lobes. The mass exhibits encroachment to the adjacent jugular veins **(A)** as well as the SVC **(B)**. There is also a pneumothorax along with multiple pulmonary bleb and bullae with thin septations **(C)** and hepatomegaly with multiple cysts **(D)**.

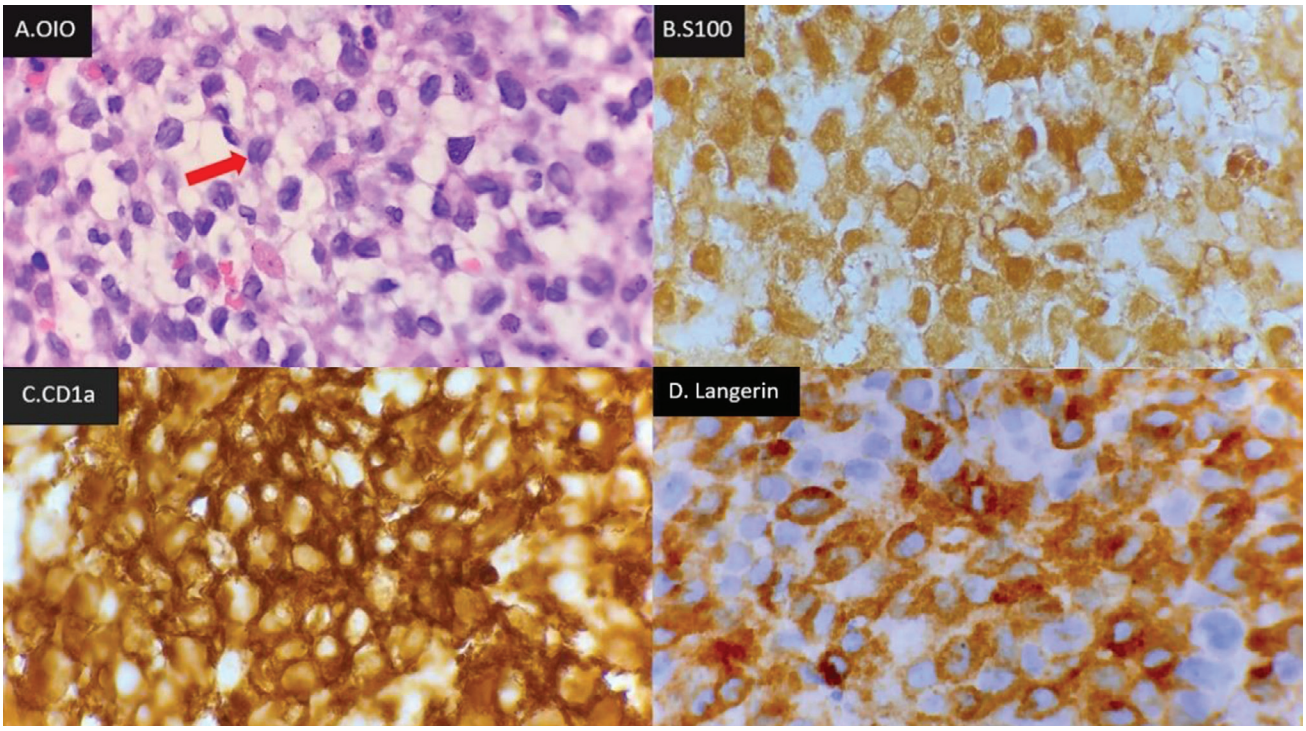

Figure 3. Photomicrographs of an oil power objective showing oval neoplastic cells with grooved nuclei *(red arrow)* with abundant amphophilic to eosinophilic cytoplasm **(A)**, S100 stain showing strong diffuse nuclear and cytoplasmic positivity **(B)**, CD1a stain showing strong diffuse membranous positivity **(C)**, and positive Langerin staining **(D)**.

DISCUSSION

LCH as a cause of goiter is rare, as the most common cause of goiter worldwide is iodine deficiency. Other causes may be natural goitrogens, smoking, autoimmune disorders, drugs rich in iodine, environmental agents, thyroid cancer and infiltrative diseases of the thyroid.[4,5]

LCH commonly presents as a tumor, skin rash, lytic bone lesions, pneumothorax, interstitial lung disease, or central diabetes insipidus. Microscopically, lesions consist of large histiocytes with abundant cytoplasm intermixed with lymphocytes and eosinophils.[6] In the "Activated-Immature model," LCH is thought to come from pathologic epidermal Langerhans cells that undergo malignant transformation or multiply because of immune dysregulation and form lesions in different organs. However, a newer proposed model called "The Misguided Myeloid Dendritic Cell Precursor Model," hypothesized that LCH lesions could come directly from bone-marrow-derived dendritic cell precursors which migrate to site of LCH lesions and differentiate into $CD207^{+}$ cells. Gene expression profiling of the pathologic cells seen in LCH showed that their profile is closer to immature dendritic cells than of epidermal Langerhans cell.[7] The dendritic cell precursors come from the bone marrow and the tropism of Langerhans cell is in the epidermis. This may explain why LCH is more common in the skeletal and integumentary system. The most common mutation identified in LCH is BRAF V600E, the presence of which correlates with multisystemic disease and poor survival.[8]

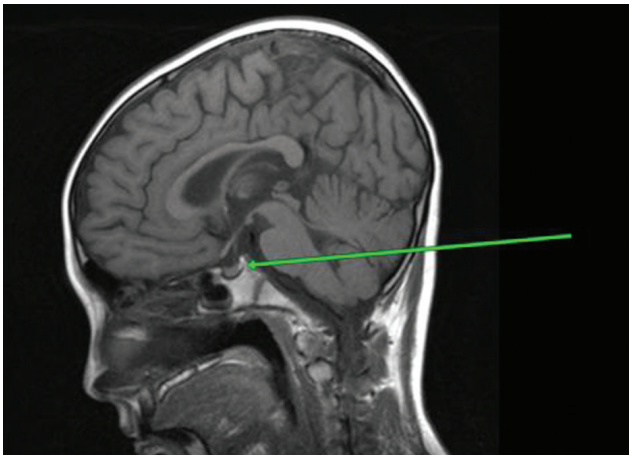

Figure 4. Midline sagittal T1 weighted image demonstrates the normal posterior pituitary bright spot.

LCH may develop in any tissue, but an incidence study showed that it most commonly affects bone, skin, and lymph nodes.[2] Seventy-five cases of adults and children with thyroid involvement in LCH have been reported. There were more cases in adults than in children (47 adults and 18 children),[9] and thyroid involvement is part of multisystemic LCH in the majority of cases; solitary involvement of the thyroid gland in LCH is extremely rare. It may present as goiter due to LCH infiltration in the thyroid.[10] Although the cause of thyroidal LCH is unclear, it is likely that encapsulation of the thyroid contributes to the rarity of its involvement. Proliferation of LCH in the thyroid often extends beyond the capsule which leads to its adherence to the surrounding structures.[11]

In the review of cases, a 38-year-old female presented with goiter and histopathology was consistent with LCH. Chest computed tomography showed bilateral multiple peripheral small nodules. Abdominal CT scan showed hepatomegaly with diffusely increased hepatic density.[12] Another 29-year-old female had LCH with thyroid, lung, and liver involvement. She also had diabetes insipidus, with polyuria being her chief complaint. She was treated with chemotherapy resulting to reduction in goiter size.[13]

When patients present with thyroid enlargement, thyroid function tests are part of the work up. Thyroid ultrasonography is especially important in those with palpable thyroid nodules, gland asymmetry, or suspicious cervical lymphadenopathy. Further evaluation with FNAC may be warranted depending on the size and ultrasound characteristics of thyroid lesion.[14]

In this patient, thyroid carcinoma was highly considered in the background of a rapidly enlarging neck mass associated with weight loss. FNAC showed a moderately cellular aspirate with abundant scattered large monomorphic atypical cells with increased nuclear-to-cytoplasmic ratio, scant cytoplasm, irregularly-shaped nuclei and inconspicuous nucleoli. The atypical cells form occasional microfollicles and are admixed lymphocytes in a background of colloid. During this time, a solitary thyroid lesion was considered, but the current involvement of the lungs and liver was not yet known.

The Bethesda System for reporting thyroid cytopathology favored category IV which is suspicious for follicular neoplasm. The recommendation for this lesion is surgical excision, but molecular testing may also be done to supplement risk assessment before doing surgery.[15] During admission, the patient had other manifestations such as pulmonary blebs and hepatic cysts, signs that the disease was not limited to the thyroid.

The diagnosis of thyroid LCH can be difficult. Fine needle aspiration can be useful in the diagnosis but Langerhans cells can still be misinterpreted as some other cells.[10] The diagnosis of LCH on FNAC may pose a challenge to the cytopathologist due to its rarity, low clinical index of suspicion, and overlapping cytologic findings in more common primary thyroid pathologies.[16] A similar case was published where the initial cytological interpretation of the thyroid FNA suggested a follicular neoplasm but histopathology after subtotal thyroidectomy revealed LCH. Thyroid LCH could be easily mistaken as undifferentiated carcinoma, lymphoma, lymphocytic thyroiditis, chronic granulomatous thyroiditis, and cystic degeneration of multinodular goiters. Immunohistochemical reactivity of histiocytes of S100 and CD1a is useful in diagnosing a case of LCH.[17]

LCH with thyroid involvement can be solitary or part of multisystem LCH. There are cases reported where the thyroid is the only organ involved in LCH.[16] Hence, in patients with a solitary goiter, LCH should also be included in its possible causes. Others report cases of LCH of the thyroid with a concomitant thyroid carcinoma.[18,19] In this patient, there was no evidence that a concomitant thyroid carcinoma exists.

LCH involving the thyroid gland may present with different states of thyroid dysfunction. In a review of sixty-six cases, majority are euthyroid (40.9%), followed by hypothyroid (19.7%), and less commonly, some have subclinical hypothyroidism (10.6%) or subclinical hyperthyroidism (1.5%).[9] This patient was initially euthyroid but developed subclinical hypothyroidism with the rapidly enlarging goiter. With prompt initiation of chemotherapy, thyroid function reverted to normal and prolonged levothyroxine treatment was avoided.

After confirming the diagnosis of thyroid LCH, work up for other systemic involvement should be done. Thoracic CT scan, abdominal ultrasonography, bone scan, and bone marrow aspiration can distinguish single organ involvement from multisystemic disease.[20] For this patient, a CT scan of the cranium and abdomen, along with bone marrow aspiration with biopsy ruled out cranial and bone marrow involvement, but confirmed the presence of cystic lesions in the lungs and liver.

Treatment depends on whether LCH is solitary or with multisystem involvement. For primary thyroid LCH, treatment options are surgery, chemotherapy or a combination of surgery with adjuvant chemotherapy.[9] Multisystemic LCH treatment includes vinblastine 6 mg/m^2 intravenously weekly bolus for 6 weeks and prednisone 40 mg/m^2/day given orally in three divided doses for 4 weeks which is then tapered over the next two weeks. Patients undergo reevaluation after the first 6 weeks of treatment, and treatment may be continued depending on the assessment.[21] Majority of children with thyroid LCH received combination of surgery and chemotherapy.[9] This patient with multisystemic LCH received chemotherapy based on the LCH-II study consisting of prednisone 40 mg/m^2/day and vinblastine 6 mg/m^2 intravenously weekly bolus for 6 weeks.

Prognosis of LCH depends on the presence of risk organ (i.e., bone marrow, liver, and spleen) involvement and response to initial systemic therapy. Patients with single-system disease have an excellent prognosis, with a survival rate of almost 100%, with a 5-year recurrence rate of <20%, usually involving the same organ system. On patients with risk organ involvement at diagnosis, the projected survival is 77%.[22] This patient had liver involvement but had good response to initial chemotherapy.

CONCLUSION

LCH as a cause of goiter is rare. In children, it is most commonly part of a multisystemic LCH rather than a single system. Being unaware that LCH may present as an anterior neck mass may lead to misdiagnosis. A high

index of suspicion and the help of a multidisciplinary team is needed for proper diagnosis and timely treatment.

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Ethical Consideration
Parental consent was obtained before the submission of the manuscript.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
KMB: Data Curation, Writing - original draft preparation, Writing - review and editing, Visualization; **MJC:** Data Curation, Visualization; **CS:** Data Curation, Writing – review and editing, Visualization, Supervision, Project administration; **EF:** Data Curation, Visualization, Supervision; **MM:** Data Curation, Visualization, Supervision; **LA:** Data Curation, Writing – review and editing, Visualization, Supervision, Project administration.

Author Disclosure
The authors declared no conflict of interest.

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