Langerhans Cell Histiocytosis of Thyroid Gland in a Child: A Case Report and Literature Review

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Introduction

Langerhans cell histiocytosis (LCH) is a rare neoplastic disease of dendritic cells with indefinite etiology and pathogenesis. The incidence rate of the disease is 4.0–5.4 per 1 million individuals, and the mortality rate is about 3% in adults. LCH is often encountered in pediatric patients and can be observed as single-organ involvement or multisystemic disease. The disease affects almost every organ in the body, including bone, skin, lung, lymph nodes, hypothalamopituitary axis, liver, spleen, and other sites. When it occurs in children, it is often accompanied by multisystemic involvement. Because of its rarity, LCH with involvement of the thyroid gland can cause delays in diagnosis and misdiagnosis.

Case Report

A 10-year-old boy was admitted to our clinic who had enlarged neck masses for 3 months. The patient had dyspnea, especially in sleep, and moderate dysphagia with solid foods. He had no fever, hoarseness, nausea, vomiting, or palpitations. Physical examination revealed a 5-cm non-tender mass over the anterior right neck and soft and matted cervical lymph nodes greater than 2 cm (Figure 1). Other system examinations were normal. The patient had no known illness and did not have a family history of thyroid disease and malignancy. Laboratory investigation showed that serum thyroid stimulating hormone was 11.8 mU/L (normal range, 0.4–4.2), free thyroxine was 5.53 pmol/L (normal range, 11.4–22.6), free triiodothyronine was 2.87 pmol/L (normal range, 3–6.7), serum thyroglobulin (Tg) was 393.6 ng/mL (normal range, 0–50), and anti-Tg and anti–thyroid peroxidase were negative. There was no abnormality in complete blood count or kidney and liver function tests. Erythrocyte sedimentation rate, lactate dehydrogenase, and urine analysis were normal. Ultrasonography (USG) of the neck revealed a 5.2 × 3 cm irregularly edged nodule with microcalcifications in the right lobe of the thyroid gland and hilus-erased lymphadenopathies greater than 2 cm in the right lateral neck (Figure 2). USG-guided fine-needle aspiration biopsy (FNAB) was performed on the thyroid nodule. The biopsy was reported as anaplastic epithelial tumor and/or histiocytosis: atypical lymphoid proliferation with no definitive discrimination. Afterward, the patient was investigated for systemic involvement. Computed tomography (CT) of the thorax demonstrated fine-walled bullae up to 6 cm in both lungs with a mid-to-upper lung zone predominance, no interstitial involvement, bilateral pneumothorax, and mediastinal lymphadenopathies up to 2.5 cm. There were no pathological findings on abdominal USG and CT. No evidence of disease involvement was found in the bone survey.

Considering the presence of compression symptoms, right lobectomy of the thyroid gland and excisional lymph node biopsy were performed. Pathology findings showed proliferation of Langerhans cells with nuclear grooves in a background of dispersed eosinophils. Immunohistochemical staining for CD1a and S100 were positive, and LCH was diagnosed. The BRAF V600E mutation was not detected by direct DNA sequencing.

The patient subsequently underwent chemotherapy, including vinblastine. Induction therapy was a dose of 6 mg/m² every 7 days in combination with prednisone for 6 weeks, and mainte-
Table 1. LCH Cases Presented with Thyroid Gland Involvement Published in the English Literature in the Last 5 Years

| Year | Author et al. | Age (Years) | Site | TSH, μIU/mL | fT4, pmol/L | fT3, pmol/L | BRAF Mutations | Other Thyroid Pathology | Treatment | Outcome |
|------|--------------|-------------|------|-------------|-------------|-------------|---------------|------------------------|-----------|---------|
| 2016 | Kuhn et al.  | 73          | F    | NR          | NR          | NR          | NR            | BRAF V600E (+)         | Thyroidectomy | Alive   |
| 2016 | AlZahrani et al. | 27         | F    | 0.01        | 13.7        | 3.1         | NR            | None                  | Total thyroidectomy, RAI, chemotherapy | Alive     |
| 2017 | Wu et al.    | 40          | M    | NR          | NR          | NR          | NR            | None                  | Right lobectomy, methotrexate, ara-c | Alive     |
| 2017 | Al Hamad et al. | 36         | F    | NR          | NR          | NR          | BRAF V600E (+) | PTC, lymph node, lung, liver, spleen | Total thyroidectomy, etoposide, prednisone | Alive     |
| 2018 | Yokoyama et al. | 3           | F    | 20.17       | NR          | NR          | None          | Lung                  | Induction with ADR, VCR, and PSL (progression) | Alive     |
| 2019 | He et al.    | 3.5         | M    | 87.8        | 0.26        | 2.92        | BRAF V600E (+) | None                  | PSL, JLSG-96 induction chemotherapy, vemurafenib | Alive     |
| 2019 | Zaidi et al. | 31          | M    | 3.5         | 13.7        | 3.1         | BRAF V600E (+) | None                  | Thyroidectomy, RAI | Alive   |
| 2019 | Nacef et al. | 37          | F    | 45          | 9.37        | 2.92        | BRAF V600E (+) | None                  | Thyroidectomy, prednisone | Alive   |
| 2019 | Ozisik et al. | 31          | M    | 45          | 9.37        | 2.92        | BRAF V600E (+) | None                  | Thyroidectomy, prednisone | Alive   |
| 2020 | Ozisik et al. | 58          | M    | 45          | 9.37        | 2.92        | BRAF V600E (+) | None                  | Thyroidectomy, prednisone | Alive   |
| 2020 | Current case | 10          | M    | 11.8        | 5.53        | 2.87        | BRAF V600E (+) | None                  | Thyroidectomy | Alive   |

Discussion

The most common organ involvement in LCH is bones (80% of cases). It causes asymmetric osteolytic lesions in the bones and often affects the skull. Skin involvement is seen in approximately 33% of cases. The most common endocrinological abnormality in LCH is central diabetes insipidus. In approximately half of patients with LCH involving the thyroid, hypothalamic-pituitary abnormalities are observed, and usually these patients had central diabetes insipidus. In our case, no findings suggesting central diabetes insipidus were found.

Thyroid involvement in LCH usually manifests itself with nodular or diffuse enlargement of the gland (Table 1). Because of its rarity, it can be misinterpreted as benign goiters, undifferentiated carcinoma/anaplastic carcinoma, or lymphoma. It has also been shown that LCH of the thyroid accompanies primary thyroid malignancies at the same time.

Different thyroid hormone conditions can be seen in patients with thyroid LCH. Most often, euthyroid and hypothyroid statuses are detected, but subclinical hypothyroidism and subclinical hyperthyroidism are also seen. In addition, anti-Tg and antimicrosomal antibodies rarely can be determined in cases of LCH involving the thyroid.

USG and FNAB are the first methods used in the investigation of thyromegaly. Although FNA of the thyroid is useful to establish a diagnosis, it can be confused with poorly differentiated carcinoma/anaplastic carcinoma, or lymphoma. It has also been shown that LCH of the thyroid accompanies primary thyroid malignancies at the same time.

Because the patient was under the age of 18, informed consent was obtained from the parents regarding use of the data and materials to be published.
Because histopathological features may interfere with other diseases, CD1a and S100 positivity should be seen for a definite diagnosis.\(^\text{1,14}\) In some publications, it is stated that CD207 (Langerin) immunohistochemical staining will also help in the accurate diagnosis of LCH.\(^\text{11}\) When primary thyroid LCH is diagnosed, it is recommended to perform some tests, such as thoracic CT, bone scintigraphy, and abdominal USG, to determine the presence of multisystem involvement.\(^\text{3,6}\)

There are no specific guidelines for the management of patients with LCH in the thyroid. Although isolated thyroid LCH can only be treated with thyroidectomy, systemic treatment is preferred in cases with multisystemic involvement.\(^\text{5,5}\) For disseminated aggressive disease, various chemotherapeutic agents can be used, including glucocorticoids, vinblastine, etoposide, methotrexate, doxorubicin, and cyclophosphamide. Because of the frequency of occurrences, a majority of adults underwent surgery alone; however, the majority of children underwent the combination of surgery and chemotherapy for thyroid LCH treatment.\(^\text{3,7}\)

Consequently, although thyroid LCH is rarely seen, it should be kept in mind in patients with goiter. In some patients, multisystemic involvement may be overlooked and cause delays in diagnosis and treatment. In patients who cannot be diagnosed by FNAB and have compression symptoms, surgery may be useful in definitive diagnosis and treatment.

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