

Delayed Diagnosis of Langerhans Cell Histiocytosis Presenting With Thyroid Involvement and Respiratory Failure: A Pediatric Case Report

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Summary: Langerhans cell histiocytosis (LCH) is a rare disease with localized to disseminated clinical features. Thyroid involvement in LCH is rare and presenting as either a single-organ or multisystem disease, it is usually misinterpreted as another thyroid disorder. Therefore, the LCH diagnosis is often delayed. We report a pediatric case of LCH with thyroid involvement as the initial clinical manifestation progressing to respiratory failure. Clinicians should note insidious extrathyroidal laboratory abnormalities and consider infiltrative thyroid diseases, such as LCH. Systematic clinical and laboratory investigations are needed to prevent delayed diagnosis because the classic features of LCH may become evident only over time.

Key Words: thyroid, Langerhans cell histiocytosis, pediatric, delayed diagnosis

(*J Pediatr Hematol Oncol* 2020;42:e810–e812)

Langerhans cell histiocytosis (LCH) is a rare disease with clinical presentations ranging from localized to disseminated features. Any organ or system can be affected by LCH. When the thyroid is involved, LCH may present with a solitary nodule, a nodular goiter, a diffuse goiter, or lymphocytic thyroiditis.^{1–3} LCH usually occurs as a part of a multisystem disease in children.^{4,5} Because of its rarity, thyroid LCH is often misinterpreted as other common entities of thyroid disease and thereby results in delayed diagnosis.^{6–10} Many general pediatricians may be unable to recognize the pattern of LCH as the lead clue for diagnosis. Therefore, we report a case of a pediatric patient who experiences apparently isolated thyroid involvement as the first manifestation of LCH. An LCH diagnosis was confirmed by a lymph node biopsy when severe systemic complications occurred during the late stage of the disease. Although thyroid LCH in children is rare, missing and delayed diagnosis may yield undesirable outcomes. Indeed,

in the case presented here, progression to a more aggressive stage required more intensive treatment.

CASE

On September 16, 2017, a 3.5-year-old boy was transferred to our emergency department with difficulty in breathing for 4 days. Upon arrival, he exhibited remarkable respiratory distress with a respiratory rate of 60 to 70 bpm and low oxygen saturation of 85%. He had a temperature of 38.5°C and a pulse of 140 to 150 bpm. Arterial blood gas values were as follows: pH, 6.92; PaCO₂, 12.52 kPa; and PaO₂, 5.53 kPa on 8 L/min oxygen. He was intubated for supportive ventilation immediately.

The patient had a 9-month history of a neck mass that gradually enlarged and was believed to be primary thyroid goiter with hypothyroidism. He was subsequently prescribed levothyroxine replacement therapy. We also noted a slight elevation in his liver enzymes throughout his disease course. He did not have a family history of thyroid disease or hepatitis. On physical examination, he had a diffusely enlarged nontender thyroid gland extending bilaterally, seborrheic dermatitis-like lesions on his scalp, bilateral cervical lymphadenopathy, and hepatosplenomegaly. No obvious bronchovesicular sounds were auscultated over the lung fields.

Laboratory studies revealed hypothyroidism: thyroid-stimulating hormone (TSH) level, 87.8 μIU/mL; free T4, 10.36 pmol/L; and free T3, 2.92 pmol/L. Antithyroid antibodies were negative. Other laboratory tests revealed mild anemia (hemoglobin, 95 g/L); marginally elevated platelet counts (642 × 10⁹/L); and increased serum alanine transaminase (102 IU/L), aspartate transaminase (158 IU/L), lactate dehydrogenase (460 U/L), and gamma-glutamyl transferase (443 U/L). A chest radiograph revealed reticular and nodular opacities in the middle to upper lung zones. Ultrasonography of the neck showed bilateral heterogenous enlarged thyroid lobes (Fig. 1A) and bilateral enlarged cervical lymph nodes with altered echoes (Fig. 1B). Computed tomography of the neck and chest demonstrated mild tracheal compression caused by the enlarged thyroid glands (Fig. 2A) and multiple thin-walled air cysts of varying size, with a mid-to-upper lung zone predominance and interstitial thickening (Fig. 2B). Computed tomography of the abdomen showed diffuse hepatomegaly with multiple cyst-like lesions throughout the liver parenchyma (Fig. 2C). Brain magnetic resonance imaging, whole-body bone scintigraphy, and bone marrow aspiration revealed no abnormal findings. On the basis of these clinical and imaging results, we suspected LCH or lymphoma and performed an excision biopsy of the cervical lymph nodes. Histologic examination confirmed a definitive diagnosis of LCH on September 19, 2017.

Immunohistochemistry analysis of the excised lymph node biopsy specimen showed that most of the lymph node architecture was destroyed and replaced by extensive aggregates of enlarged mononuclear cells admixed with numerous eosinophils and histiocytes. These mononuclear cells were characterized by reniform nuclei, nuclear grooves, and an abundance of pale-pink cytoplasm. The mononuclear cells also demonstrated strong positivity with S100, CD1a, and Langerin immunohistochemical stains. The *BRAF*^{V600E} mutation was not detected by direct DNA sequencing.

Received for publication May 11, 2019; accepted September 16, 2019.
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The authors declare no conflict of interest.

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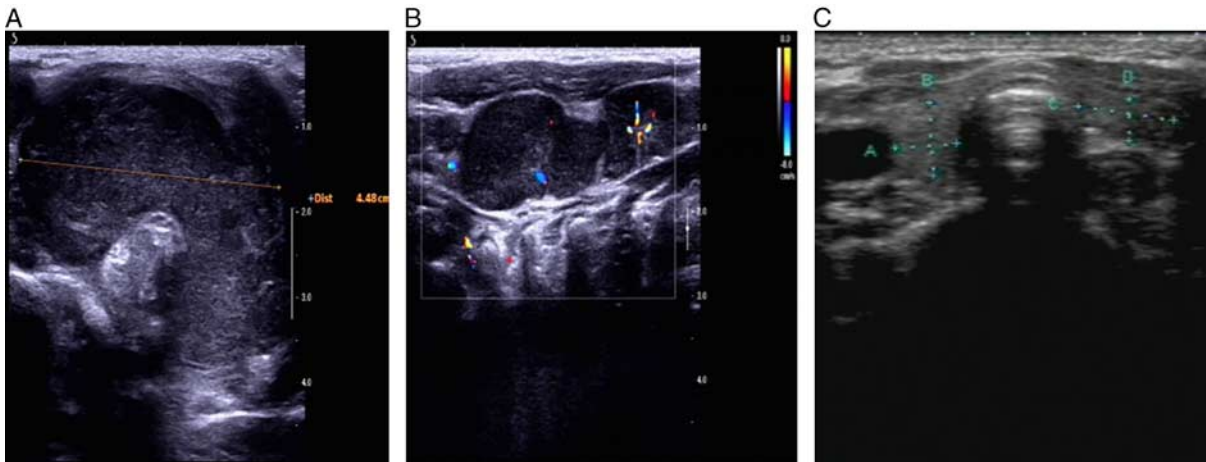


FIGURE 1. Ultrasonography showing enlarged thyroid lobes and massive cervical lymph nodes (A, B) and thyroid size recovery after 10 months of treatment (C).

Therefore, a final diagnosis of LCH with multisystem (ie, thyroid, lymph node, lung, liver, spleen, and skin) involvement was confirmed.

We administered prednisolone and the chemotherapy regimen directed by the Japan LCH Study Group (JLSG)-96 induction—a protocol because of the presence of mild airway compression and pulmonary infiltration. The patient was gradually weaned from ventilation and extubated 10 days after the excision biopsy procedure. The enlarged thyroid dramatically reduced in size and returned to normal size after 10 months of chemotherapy (Fig. 1C). TSH levels returned to normal range after 6 weeks of chemotherapy induction. He had no active disease for 10 months; however, his LCH symptoms reactivated at the 12-month follow-up with recurrent raised serum TSH and gradually decreased hemoglobin. Considering that alternating genes might mutate and contribute to the activation of the RAS-RAF-MAPK pathway, despite the absence of *BRAF*^{V600E} mutation in this patient, we added a MAPK-targeted therapy vemurafenib to the chemotherapy regimen to block the MAPK signaling pathway downstream of BRAF. To date, the patient’s condition remains improved and he receives close follow-up examinations.

DISCUSSION

We present a case of LCH with thyroid involvement as the initial clinical manifestation and progression to mild upper airway compression and respiratory failure. A diagnosis of LCH was not initially considered until most of the

classic LCH features, including seborrheic-like dermatitis, lymphadenopathy, pulmonary infiltration, and hepatosplenomegaly, occurred in the later course of the disease.

Thyroid involvement in LCH is rare, with only ~75 cases reported in both adults and children.¹ Thyroid LCH is difficult to differentiate from other common thyroid disorders because goiter, disrupted thyroid hormone status, antithyroid antibodies, and sonographic findings are similar in many diseases affecting the thyroid gland.^{11–13} Therefore, diagnosing LCH of the thyroid is extremely challenging, specifically in cases with isolated thyroid involvement. Children with thyroid-involved LCH often have other organ systems affected. However, when the classic features of LCH do not manifest at the same time as that of thyroid dysfunction, it can hinder clinician judgment. In our case, clinicians failed to establish an association between persistent, although slight, liver function impairment with underlying multiorgan involvement when interpreting these results. The factors that contributed to the rapidly progressive respiratory failure were respiratory tract infection in addition to myxedema in the airway because of hypothyroidism, cervical lymphadenopathy, and most importantly pulmonary infiltration most likely related to LCH. Moreover, the upper airway compression caused by the enlarged thyroid may have also worsened the respiratory failure to some extent.

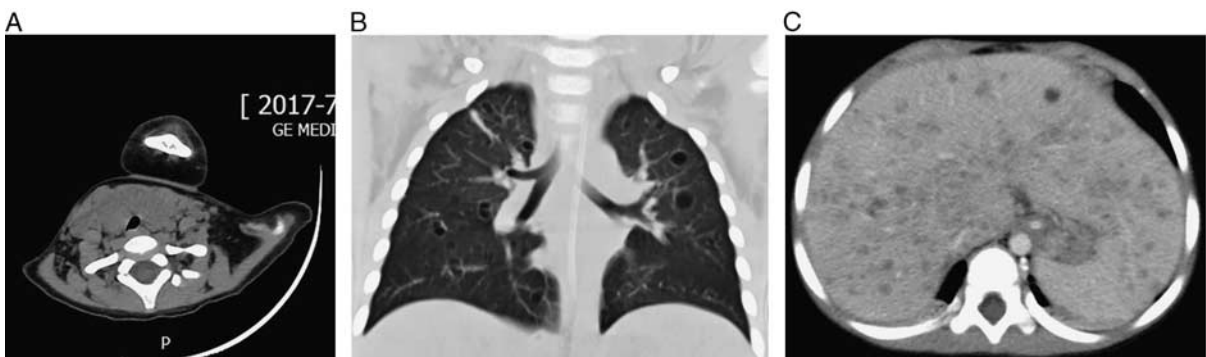


FIGURE 2. Neck, chest, and abdomen computed tomography images demonstrating mild tracheal compression caused by enlarged thyroid glands (A), multiple thin-walled air cysts of varying size with a mid-to-upper lung zone predominance (B), and diffuse hepatomegaly with multiple cyst-like lesions throughout the liver parenchyma (C).

Our experience suggests that delayed LCH diagnosis may result in undesirable clinical complications. Indeed, delayed diagnoses of LCH are not uncommon and may be attributed to several factors. First, LCH may have non-specific clinical presentations, such as diverse cutaneous manifestations,¹⁴ diabetes insipidus,¹⁵ extensive abdominal involvement,¹⁶ and other presentations depending on the affected organ systems. Second, clinicians failed to detect the classic signs and symptoms that are suggestive of LCH. Consequently, in some cases of LCH, disease progression and affected organ system dysfunction may lead to potentially life-threatening complications, such as hemophagocytic lymphohistiocytosis.¹⁷ In our case, the patient may have been on a trajectory toward active or progressive LCH with subsequent multisystem involvement. Therefore, early identification and treatment of LCH are critical to improve clinical outcomes. A definitive diagnosis of LCH generally requires a thorough clinical evaluation of patient history, characteristic symptoms, and most importantly biopsy of the involved tissue. In our case, the pathologic-based diagnosis was made by analysis of lymph node biopsy specimens as an alternative to thyroid gland tissue because it is more feasible and less invasive.

The pathogenesis of thyroid disease secondary to LCH remains unknown. A family history of thyroid disease is a reported risk factor for LCH.¹⁸ The composition of LCH lesions was first described in 1893 and includes large histiocytes with abundant cytoplasm intermixed with lymphocytes and eosinophils.¹⁹ The lesion microenvironment contains inflammatory infiltrate of T cells, macrophages, eosinophils, neutrophils, B cells, plasma cells, and multinucleated giant cells, which suggests that immune regulation failure is an important factor in LCH development and progression.²⁰ Of note, some primary thyroid diseases, such as Graves disease, chronic autoimmune thyroiditis, or papillary thyroid carcinoma, induce an apparent heavy lymphocytic infiltration.^{21,22} Therefore, it is plausible that the 2 disorders are related in fundamental ways that are consistent with their appearance and shared susceptibility genes, such as certain *BRAF* alleles.

In conclusion, this case report emphasizes that LCH in children can manifest with thyroid symptoms alone and may be challenging to diagnose, thus resulting in undesirable clinical complications. In cases of thyroid disease in which disease progression cannot be attributed to the diagnosis, clinicians should reevaluate their patients for the classic features of LCH, note laboratory findings of multiorgan system involvement, and revisit the differential diagnosis for LCH. Once LCH is suspected, a biopsy of the affected tissues and investigation of the other involved organs must be promptly conducted.

ACKNOWLEDGMENTS

The authors would like to thank Dr Nisha Badders from St. Jude Children's Research Hospital for the scientific editing of the manuscript. The authors would also like to thank Dr Ibrahim Qaddoumi for his support on this project.

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