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A rare cause of goiter: Langerhans cell histiocytosis of the thyroid

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Abstract. Goiter is a very common clinical problem; however, Langerhans cell histiocytosis (LCH) with thyroid involvement that presents as a goiter is very rare. In this article, we report one case of thyroid LCH. An 18-year-old male patient presented with goiter, polyuria, polydipsia, and lymphadenectasis of the neck, and LCH was confirmed by a lymph node biopsy and pathological investigation. Without a thyroidectomy, the goiter shrank after nine cycles of chemotherapy. In addition, we summarize the reported thyroid LCH cases in the literature from the last 10 years. LCH usually involves other organs, such as the lungs, bones, skin, pituitary gland, and lymph nodes. Thyroid LCH is more common in adults than in children, and it may coexist with a thyroid carcinoma. Without any unique thyroid manifestations, either clinically or by imaging, it is difficult to distinguish thyroid LCH from other thyroid diseases. Pathology is the gold standard for the diagnosis of LCH. A fine needle aspiration biopsy (FNAB) may help to diagnosis LCH, although sometimes it leads to misdiagnosis. Chemotherapy is recommended for multi-system LCH. Younger patients with widespread disease or who are non-responsive to chemotherapy have poor outcomes.

Key words: Langerhans cell histiocytosis, Thyroid, Goiter, Diabetes insipidus, Lymphadenectasis

GOITER is a common clinical symptom, which usually can be considered as Hashimoto's thyroiditis, endemic goiter, thyroid lymphoma, thyroid carcinoma and lymphoid tuberculosis. However, Langerhans cell histiocytosis (LCH) of the thyroid, which presents as a goiter, is rarely considered.

LCH is a monoclonal disease with an unknown etiology that is characterized by an abnormal proliferation of the Langerhans cells, which originate from bone marrow-derived dendritic cells [1]. The clinical presentation of LCH is highly variable because it can involve many organs, such as the skin, bones, lungs, pituitary gland and lymph nodes, and it can present as a single-system disease or a multi-system disease [2]. Thyroid involvement in LCH is very rare. Only 29 cases can be found in the English literature in the previous 10 years. Without the unique manifestation of an enlarged thyroid, the diagnosis of thyroid LCH is often missed or delayed. Here, we report a case of thyroid LCH, which presented as a goiter, accompanied by diabetes insipidus and lymphadenectasis of the neck and summarize the clinical manifestations, imaging, treatments and prognosis of thyroid LCH in the literature from the last 10 years.

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Case Report

An 18-year-old Chinese male came to our hospital with a neck mass that had been present for more than one year. One year before admission, the patient had discovered a mass on the left side of his neck that measured 4×3 cm. The mass was painless, and palpitations, appetite changes, hyperactivity, weight loss, dyspnea, cold intolerance and fatigue were not observed. Thyroid function showed hypothyroidism based on the following hormone levels: free triiodothyronine (FT_3): 1.98 pg/mL (normal: 2.2-4.2); free thyroxine (FT_4):0.53 ng/dL (normal: 0.8-1.7) and TSH: >100 mIU/L (normal: 0.35-3.50). Levothyroxine (at a dose titrated to 75 μg/d) was prescribed, and the thyroid function returned to normal; however, the neck mass enlarged progres-

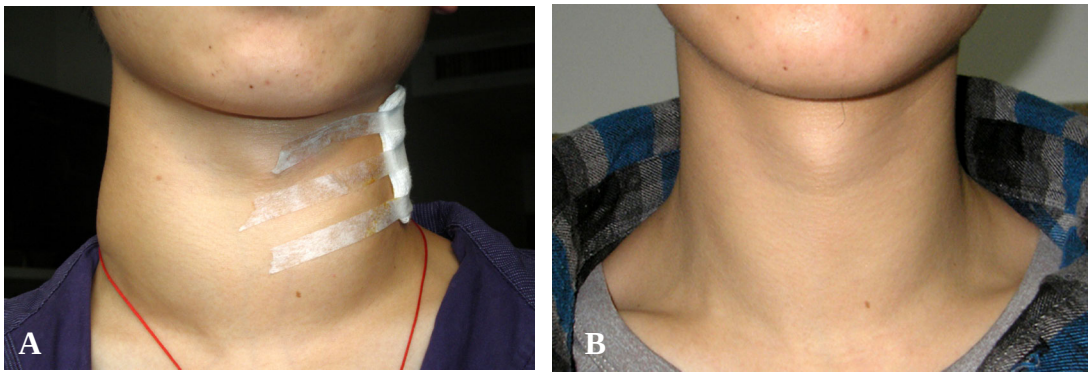

Fig. 1 Pretreatment and follow-up photographs of the patient's neck. A: The enlarged thyroid before chemotherapy. The biopsy of lymph node had been done, and the gauze was on his left neck. B: Three months after chemotherapy, the thyroid was shrunk significantly.

sively into the bilateral thyroid gland. Two months before admission, the patient experienced hoarseness and dysphagia.

Eight months before admission, he experienced polyuria and polydipsia and excreted 9000 mL of urine a day. At a local hospital, a water-deprivation test was found to be positive, and diabetes insipidus was diagnosed. The patient was administered desmopressin (0.2 mg/d), and the symptoms went into remission. He did not have a family history of thyroid disease.

On physical examination, he appeared healthy. A neck examination revealed a diffuse goiter with a smooth surface that was rubbery, non-tender, and immobile and lacked bruits. Several confluent lymph nodes on the right side of his neck could be palpated. On the left side of his neck, a lymph node measuring 1.5×2 cm was palpated (Fig. 1A). His growth was normal, and the skin, bones, heart, lungs and abdominal exams were unremarkable.

The thyroid function test results were as follows: total triiodothyronine (TT_3) was 2.0 nmol/L (normal: 1.0-3.2); total thyroxine (TT_4) was 175 nmol/L (normal: 70-180); FT3 was 6.6 pmol/L (normal: 3.2-9.2); FT4 was 24 pmol/L (normal: 8.6-26.0); TSH was 10 mIU/L (normal 0.3-5.0); and the anti-thyroglobulin (TgAb) and anti-thyroid microsomal antibodies (TMAb) were negative. Routine laboratory exams, a sex hormones test and a cortisol circadian rhythm test were normal. The chest computed tomography (CT) scan showed multiple thin-walled cavitary nodules in both lungs (Fig. 2A), while an X-ray of the lung was normal. Ultrasonography revealed a thyroid enlargement, especially in the isthmus, with heterogeneous hypoechogenicity. Radioisotope defects in the bilateral lobes were revealed by Technetium 99m thyroid scan. A contrast-enhanced CT also showed a diffusely enlarged thyroid gland with multiple confluent lymph nodes in the right side of the neck and several lymph nodes in the left carotid sheath (Fig. 2B). Magnetic resonance imaging (MRI) of the pituitary gland revealed the absence of a posterior pituitary bright spot on the T1-weighted images (Fig. 2C). An abdominal ultrasound and a skeletal radiograph survey were normal. A biopsy of the neck lymph node revealed proliferated Langerhans cells with infiltrated eosinophils (Fig. 3A) and positive immunohistochemical staining for CD1a, S-100 and CD68 (Fig. 3B, 3C, 3D). Based on the unique pathological examination, a diagnosis of LCH was established.

The patient was administered chemotherapy with vincristine (2 mg on the first day of each week for weeks 1-4, then the first day of every third week) combined with prednisone (60 mg/d that was reduced after one week with a 10 mg reduction per week for a total of six weeks, then 60 mg/d for one week when the patient was given vincristine). The patient underwent one-week treatment cycles for a total of nine cycles of chemotherapy. In addition, the patient took desmopressin (0.2 mg/d) for diabetes insipidus and levothyroxine (100 μg/d) for hypothyroidism with normal thyroid function. The large thyroid significantly shrunk within three months after the end of chemotherapy (Fig. 1B). However, the lesion in the lungs had not improved. On a contrast-enhanced CT of the neck, the thyroid was significantly smaller without any enlarged lymph nodes (Fig. 2D). A CT scan of the chest showed multiple thin-walled cavitary nodules in both lungs, which was similar to the previous examination. We recom-

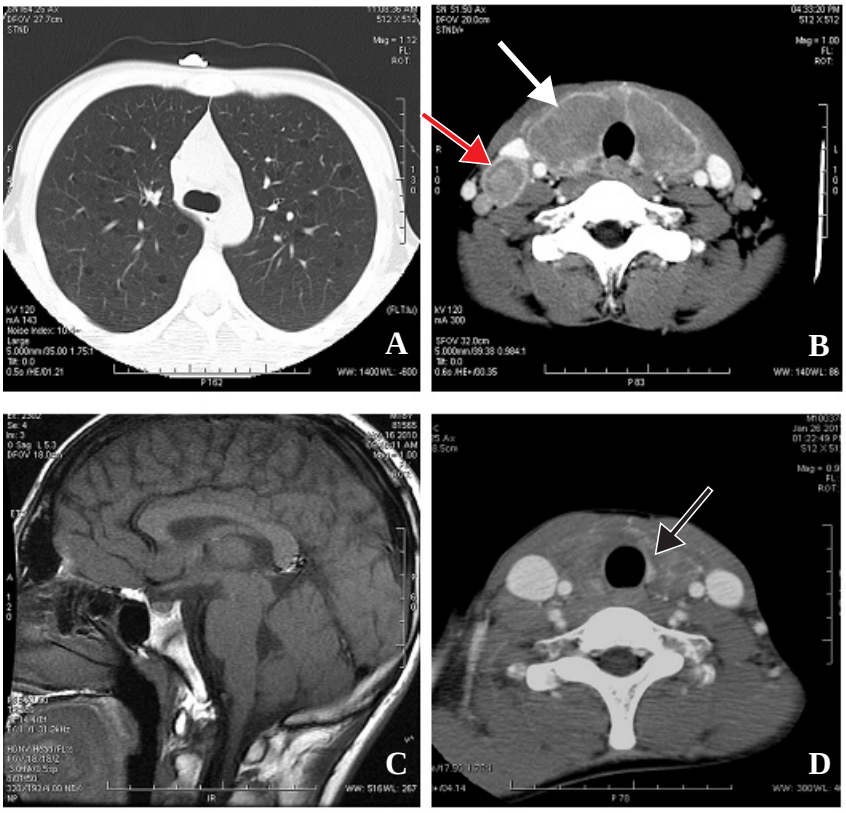

Fig. 2 Imaging examination of the patient. A: Before chemotherapy, CT scan of chest showed multiple thin-wall cavitated nodules in both lungs. B: Before chemotherapy, contrast-enhanced CT scan of thyroid showed enlarged thyroid with multiple lymph nodes. The white arrow represented enlarged thyroid, the red arrow represented confluent lymph nodes. C: Before chemotherapy, MRI image of pituitary revealed absent posterior pituitary bright spot on T1 weighted images. D: Three months after nine cycles of chemotherapy regimen with vincristine plus prednisone, contrast-enhanced CT showed thyroid was significantly shrunk (the black arrow showed), without any enlarged lymph nodes.

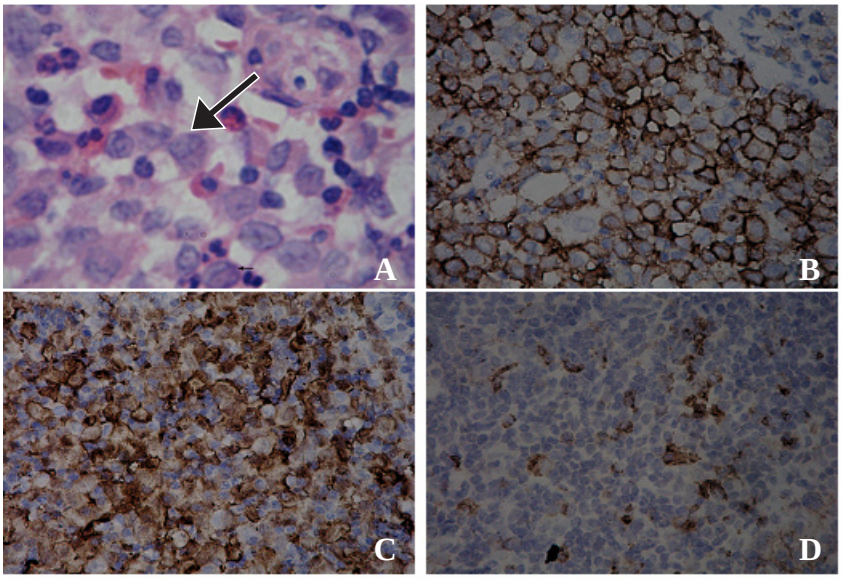

Fig. 3 Histology and immunostaining of lymph node. A: Hematoxylin and Eosin staining (×400) revealed Langerhans cells proliferated, with eosinophils infiltrated. The black arrow represented one of proliferative Langerhans cells. B: Immunohistochemical staining of CD1a was positive (×200). C: Immuno- histochemical of S-100 was positive (×200). D: Immuno- histochemical of CD68 was partly positive (×200).

mended that the patient continue chemotherapy, but his parents refused. He is still in follow-up.

Literature Review

An internet PubMed search and a China National Knowledge Infrastructure (CNKI) search were performed for the literature review with the key words "Langerhans cell histiocytosis, goiter and thyroid". A total of 38 cases [3-33] of LCH involving the thyroid were reported in the literature from 2001 to 2011. Nine cases were reported in the Chinese literature (including the current case), and 29 cases were reported in the English literature.

In our review, thyroid LCH occurred in all age groups, from 5 months to 55 years of age. There were 28 adult cases, and the male:female ratio was 1:1.8. Ten cases involved children, in which the male:female ratio was 3:2. Thyroid LCH is much more common in adults than in children, especially for females. However, thyroid LCH is more likely to affect male children than females.

Clinical presentation

The common clinical features of the reviewed cases were goiters or neck masses with about 76.3% of the patients presenting with a goiter as the first symptom. Other symptoms that also appeared first in some patients, included polyuria, polydipsia, growth retardation, amenorrhea, skin lesions and hearing loss [5, 9, 11, 25]. An enlarged thyroid can extend into the trachea leading to dyspnea [18]. All of the cases presented with obvious goiters that were rubbery, non-tender and immobile, but the presence of nodules varied.

Thyroid function

A total of 35 patients (approximately 92.1%) underwent thyroid function examinations. Eighteen patients were euthyroid, 16 patients were hypothyroid and one patient was hyperthyroid. Of the euthyroid patients, four tested positive for the TgAb. Of the hypothyroid patients, three tested positive for the TgAb and the thyroid peroxidase antibody (TPOAb).

Pathological and immunohistochemical findings

All of the cases were diagnosed by pathology. A fine needle aspiration biopsy (FNAB) was conducted in 21 patients, five patients underwent a thyroid biopsy, one patient underwent a lymph node biopsy and one patient underwent a biopsy of the granulation tissue in the external acoustic meatus, other cases were diagnosed after thyroidectomy. Our case was confirmed *via* a lymph node biopsy. Pathological findings revealed an infiltration of the Langerhans histiocytes with scattered eosinophils, neutrophils and lymphocytes. The Langerhans cell nuclei appeared to have indented grooves or were "coffee bean"-shaped, with immunohistochemical staining that was positive for CD1a, S-100 and CD68. By electron microscopy, Birbeck granules were found to be a typical feature of LCH. Thirty-three patients had undergone an immunohistochemical examination, and all stained positively for CD1a and S-100. In addition, 10 patients also tested positive for CD68, and 1 patient was positive for CD207. Electron microscopy examinations were conducted for only four patients who presented with characteristic Birbeck granules.

Imaging examination

CTs, which revealed enlarged thyroids with low-density areas, showed obvious goiters for 10 patients. Thyroid ultrasounds were performed on 18 patients and revealed hypoechoic masses. Eight patients obtained thyroid isotope scans with four showing cold nodules and one showing a non-functional mass. Fluorodeoxyglucose (FDG) positive emission tomography (PET) revealed hypermetabolic activity in the necks of two patients.

The involvement of other systems

Seven patients had isolated thyroid LCH in the cases we reviewed; however, the number may be overestimated because some cases didn't have comprehensive examinations. All of these isolated thyroid LCH cases were female, and it was more common in adults than in children with six adults and one child, who was only five months old [3, 14, 18, 26, 27, 29]. In addition to involving the thyroid, LCH usually involves other organs, such as the lungs, bones, skin, pituitary gland, liver and lymph nodes (Table 1). The lungs and pituitary gland were the organs most commonly involved with LCH. No significant differences in system involvement were found between adults and children. LCH of the lung presented as an asthma-like cough and dyspnea along with multiple cavitary nodules observed in a CT scan of the chest. When the pituitary gland was involved, the patients usually had diabetes insipidus. Rashes were found in patients with skin involvement, and biopsies of the skin lesions showed infiltration by the Langerhans histiocytes. A lymph node enlargement

Table1 Other system involvement of thyroid LCH

Organ involvement	Case	Proportion
Lung	15	48.4%
Hypothalamo-pituitary	15	48.4%
Skin	8	25.8%
Bone	7	22.6%
Lymph node	6	19.4%
Liver	5	16.1%
External ear	3	9.7%
Urinary tract	1	3.2%
Parotid gland	1	3.2%
Thymus	1	3.2%
Parathyroid glands	1	3.2%

was revealed when LCH involved the lymph node.

Treatment and prognosis

In the reviewed cases, the treatment for thyroid LCH included surgery and chemotherapy. Twelve patients underwent chemotherapy. The chemotherapeutic drugs included prednisone, vincristine, 6-mercaptopurine and methotrexate. The length of time for chemotherapy treatment ranged from 12 weeks to one year. Twelve patients underwent a total thyroidectomy or a subtotal thyroidectomy, nine patients underwent a thyroidectomy combined with chemotherapy, and two patients had a thyroidectomy combined with radiotherapy. Two patients underwent a thyroidectomy combined with chemotherapy and radiotherapy.

Twenty-eight patients were followed up for three months to eight years. Ten patients did not complete the follow-up. Symptom remission occurred in 17 cases, which presented as a shrinkage of the goiter and an alleviation of the LCH symptoms involving other organs, with six patients experiencing disease stability without progression, one patient experiencing skin recurrence of LCH and thyroid papillary microcarcinoma and one patient experiencing decreased growth velocity in the third year of follow-up.

Three patients died, including a 29-year-old man who had a multi-system LCH with thyroid papillary carcinoma. This patient's symptoms were poorly controlled following chemotherapy, and three years after the diagnosis of LCH, he died of lung disease. A five-year-old girl had multi-system LCH (pituitary, liver, and thyroid) combined with precocious puberty. She died due to unknown causes two years and four months after disease diagnosis. A ten-year-old boy refused chemotherapy after surgery, and he died of respiratory failure two and a half years after LCH was diagnosed [6, 7, 28].

Discussion

The vast majority of LCH patients are children under the age of 10 years old, but thyroid LCH is much more common in adults. The first symptom of thyroid LCH usually presents as a goiter or neck mass with or without other organ involvement. The goiter may occur before or after the symptoms of other organ involvement. Thyroid function may be euthyroid or hypothyroid depending on the degree of thyroid involvement [10]. The enlarged thyroid presents as a hypoechoic mass on an ultrasound and as a "cold nodule" or radioisotope defect in a thyroid isotope scan.

Without any unique manifestations, either clinically or by imaging, it is difficult to distinguish thyroid LCH from other thyroid diseases. For thyroid diseases that present with a goiter, Hashimoto's thyroiditis, thyroid carcinoma and thyroid lymphoma are usually considered. Hashimoto's thyroiditis, which presents as a painless neck mass, usually shows hypothyroidism or euthyroidism that is positive for TPOAb and TgAb. In the reviewed cases, two cases [5, 22] were first diagnosed as Hashimoto's thyroiditis and then were confirmed to be LCH by pathology. Hashimoto's thyroiditis that coexisted with thyroid LCH could also be seen in the cases we reviewed [16, 25, 29, 33]. These cases showed lymphocytic thyroiditis in addition to the proliferation of Langerhans cells *via* a pathological measurement. Our case can be distinguished from Hashimoto's thyroiditis by the negative TPOAb and TgAb result. Thyroid LCH cases that were misdiagnosed as thyroid carcinomas were reported in the literature recently [21]. Additionally, LCH may coexist with a thyroid carcinoma [6, 10, 16, 29]. It is possible that chronic inflammatory conditions of the thyroid induced by LCH lead to an increased risk for the development of a thyroid carcinoma [6]. LCH of the thyroid also needs to be distinguished from endemic goiter, thyroid lymphoma and lymphoid tuberculosis.

Pathology and immunohistochemical examinations are required for the proper diagnosis of thyroid LCH. The proliferation of LCH, a positive CD1a result and Birbeck granules as seen with electron microscopy are the gold standards for the diagnosis of LCH [34]. Langerin (CD207), which is expressed on the cell surface and in the cytoplasm of Langerhans cells, can specifically reflect Birbeck granules [35]. FNAB is useful for diagnosing LCH; however, misdiagnoses sometimes occur. In the reviewed cases, FNAB was per-

formed in 21 patients, and about half of the patients were misdiagnosed. Five out of 10 cases were diagnosed with thyroid carcinoma, two cases revealed no significant findings and three cases had a proliferation of atypical follicular cells. The current case presented as a goiter with enlarged neck lymph nodules, and the infiltration of Langerhans histiocytes and eosinophils that were positive for CD1a could be determined with a biopsy of the lymph nodules, so the diagnosis was established. LCH of the lymph nodules may be misdiagnosed as Rosai-Dorfman disease (RDD) [36] by pathology. RDD is a benign, histiocytic, proliferative disease that presents as an enlargement of the neck lymph nodule. RDD is characterized by an infiltration of histiocytes, lymphocytes and plasma cells. The identification of RDD and LCH depends on the results of an immunohistochemical examination. Positive S-100 and CD68 stains and a negative CD1a result without Birbeck granules are characteristic of RDD.

Multi-system involvement is a feature of LCH, and the posterior pituitary gland was affected in over half of patients, while the lungs, bones and skin are also usually involved. Our patient had goiter accompanied by diabetes insipidus, which indicated LCH, and this diagnosis was confirmed by a lymph node biopsy. Patients with posterior pituitary involvement can present with diabetes insipidus, which can occur before or after the goiter. Our patient had a goiter first and then developed diabetes insipidus. Occasionally, LCH involves the anterior pituitary, and the patient may have growth retardation or low-levels of gonadal hormones [30].

To diagnose multi-system LCH, a CT scan of the chest, a bone scan and an ultrasound or CT of the abdomen are needed. Sometimes the lesion is difficult to find and requires further examination. Our patient had no cough or asthma, and a chest X-ray was normal; however, a CT scan of the chest indicated the lungs were involved.

The treatment of LCH depends on the clinical extent and progression of the disease [33]. First, we should determine the category of LCH: single-system LCH or multi-system LCH. Single-system LCH should be determined by the number of sites involved [34, 35]. Treatment will be different depending on which organs are involved. Thyroidectomy is performed for isolated LCH of the thyroid. Patients with multi-system LCH should be evaluated for organ dysfunction and the involvement of high-risk organs (such as the lungs, liver, spleen and the hematopoietic system) [34]. Intense, long-term and combination chemotherapy is recommended for multi-system LCH [37]. The chemotherapeutic regimens include prednisone, vincristine and methotrexate. Chemotherapy combined with surgery is also a treatment option. The current case of thyroid LCH with pituitary, lungs and lymph node involvement was a multi-system LCH case combined with high-risk organ involvement; therefore, chemotherapy was more reasonable. This patient was administered chemotherapy (vincristine and prednisone, VP), which shrank the enlarged thyroid and lymph nodes significantly after nine cycles of chemotherapy, but there was no alleviation in the lungs.

The prognosis of LCH is related to the age, the number of involved organs, the function of the involved organs and the response to treatment. Younger patients with high-risk organs, patients with widespread disease or patients that are non-responsive to chemotherapy have poor outcomes [5]. Although isolated thyroid LCH may have a good prognosis after surgery, long-term follow-up is necessary because isolated thyroid LCH may involve other organs and develop into multi-system LCH [4]. In patients with refractory LCH or relapsed LCH, cladribine (2-CdA), 2-deoxycoformycin (2-DCF) and stem cell transplants may be useful [1].

In conclusion, we reported a case of thyroid LCH with multi-system involvement confirmed by a lymph node biopsy. A literature review showed thyroid LCH usually presents as a goiter or neck mass and can be easily misdiagnosed as other thyroid diseases. Therefore, in goiter patients, especially those with lungs, bones, and pituitary involvement, LCH should be considered. Patients with thyroid LCH need a CT scan of the chest, a bone scan and an ultrasound of the abdomen to determine the category of LCH and the extent of disease, which will help in determining the course of treatment.

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Conflict of Interest

None of the authors have a conflict of interest with any of the work presented.

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