

Isolated Langerhans Cell Histiocytosis of the Thyroid Gland Mimicking Thyroid Malignancy: A Diagnostic Pitfall and Literature Review, A Case Report

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Case Report

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Abstract

Background

Langerhans cell histiocytosis (LCH) is a rare clonal proliferative disorder of dendritic cell characterized by variable clinical manifestations and multisystem involvement. Thyroid involvement is exceptionally uncommon and may clinically mimic primary thyroid malignancy, creating significant diagnostic challenges.

Case presentation

We report a rare case of 35-year-old woman presenting with a progressively enlarging thyroid mass associated with dysphagia and hoarseness. Her medical history was notable for diabetes insipidus. Ultrasonography (USG) revealed diffuse enlargement of the thyroid gland with a dominant solid nodule in the left lobe. Fine-needle aspiration biopsy (FNAB) suggested a malignant lesion suspicious for lymphoma. The patient subsequently underwent total thyroidectomy for definitive diagnosis and treatment. Histopathological examination demonstrated diffuse infiltration of the thyroid parenchyma by atypical histiocytic cells with characteristic grooved nuclei admixed with numerous eosinophils and lymphocytes. Immunohistochemical analysis revealed strong positivity for CD1a and S100 protein, confirming the diagnosis of Langerhans cell histiocytosis. Further systemic evaluation showed no evidence of extra cervical involvement, establishing the diagnosis of isolated thyroid LCH. She was subsequently received adjuvant chemotherapy with cytarabine, along with levothyroxine and remained clinically stable for 6 – month follow-up period.

Conclusions

Primary thyroid LCH is an exceedingly rare entity that can closely resemble thyroid malignancy both clinically and cytologically. Accurate diagnosis relies heavily on histopathological evaluation and immunohistochemical confirmation. Awareness of this rare diagnostic possibility is important to avoid misdiagnosis and to guide appropriate systemic assessment and management.

Introduction

Langerhans cell histiocytosis (LCH) is a rare clonal neoplastic disorder characterized by the proliferation and accumulation of pathologic Langerhans-type dendritic cells within various tissues and organs. Recent molecular studies have demonstrated recurrent activation of the mitogen-activated protein kinase (MAPK) pathway, particularly involving BRAF V600E mutations, supporting the neoplastic nature of this disease. The reported annual incidence of LCH is approximately 4–5 cases per million individuals, with a wide spectrum of clinical manifestations ranging from isolated single-organ lesions to aggressive multisystem disease [1].

LCH most commonly affects the skeletal system, especially the skull and long bones, whereas endocrine involvement typically occurs in the hypothalamic–pituitary axis and frequently presents as diabetes insipidus. Thyroid gland involvement is exceptionally rare, particularly as an isolated manifestation without evidence of multisystem disease. Because of its rarity and nonspecific clinical presentation, thyroid LCH often poses a considerable diagnostic challenge and may mimic primary thyroid malignancies, including anaplastic carcinoma, thyroid lymphoma, and chronic thyroiditis, both clinically and radiologically [1].

Histopathologically, LCH is characterized by infiltration of large histiocytic cells with abundant eosinophilic cytoplasm and distinctive grooved or folded nuclei, frequently accompanied by eosinophils, lymphocytes, and multinucleated giant cells. Immunohistochemically, lesional cells typically express CD1a, langerin (CD207), and S100 protein, which are essential markers for confirming the diagnosis [2].

Due to the rarity of thyroid involvement and the potential for diagnostic misinterpretation, awareness of this entity is important for both clinicians and pathologists. Here in, we report a rare case of isolated thyroid LCH in an adult woman initially suspected to have thyroid malignancy. We further discuss the clinicopathological features, immunohistochemical findings, differential diagnosis, and relevant literature regarding this uncommon presentation.

Case presentation

A 35 - year - old woman presented with a progressively enlarging anterior neck mass over a 2- month period, associated with dysphagia, and hoarseness. She denied symptoms suggestive of hypothyroidism or hyperthyroidism, including palpitations, heat intolerance, weight loss or cold intolerance. Her past medical history was for diabetes insipidus manifested by polyuria and polydipsia. No significant family history or prior thyroid disease was reported.

Physical examination revealed diffuse enlargement of the thyroid gland, predominantly involving the left lobe. The mass was firm in consistency and moved with swallowing. No palpable cervical, axillary, or inguinal lymphadenopathy was identified.

Laboratory investigations demonstrated euthyroid function with mildly decreased free thyroxine levels (TSH: 3.06 mIU/L, FT3: 3.62 pg/mL, FT4: 0.41 ng/mL). Neck ultrasonography revealed diffuse thyroid enlargement with a dominant solid nodule measuring approximately 41mm within the left thyroid lobe. The right thyroid lobe measured 11x15x38mm, whereas the left lobe measured 33x30x55mm. No cervical lymphadenopathy was detected.

Fine needle aspiration biopsy (FNAB) suggested a malignant lesion suspicious for thyroid lymphoma. Following multidisciplinary discussion, the patient underwent total thyroidectomy for definitive diagnosis and treatment.

Intraoperatively, the thyroid gland was diffusely enlarged and densely adherent to the surrounding strap muscles and trachea, making surgical dissection technically challenging. Total thyroidectomy was successfully performed with preservation of both recurrent laryngeal nerves.

Gross pathological examination demonstrated diffuse enlargement of the thyroid gland with a firm gray-white cut surface. Microscopically, the thyroid parenchyma was extensively infiltrated by sheets of atypical histiocytic cells associated with numerous eosinophils and lymphocytes (Fig. 1). The lesional cells exhibited abundant eosinophilic cytoplasm and characteristic oval to elongated nuclei with prominent nuclear grooves and irregular nuclear contours. Destruction of normal thyroid follicular architecture was evident (Fig. 2).

Initial the histopathology interpretation suggested an unusual malignant neoplasm not typical of conventional thyroid carcinoma. Immunohistochemical analysis subsequently demonstrated diffuse strong positivity for CD1a (Fig. 3) and S100 protein in the lesional cells (Fig. 4), while focal staining for CD45, CD20, and CD3 was observed in the background inflammatory infiltrate. Based on the characteristic morphologic and immunophenotypic findings, a final diagnosis of Langerhans cell histiocytosis involving the thyroid gland was established.

Further systemic evaluation, including bone scintigraphy, revealed no evidence of skeletal or extranodal involvement. Therefore, the patient was diagnosed with isolated thyroid Langerhans cell histiocytosis. After thyroidectomy, patient was received adjuvant therapy with cytarabine, along with levothyroxine supplementation and is on regular follow – up for 6 months without any complaints.

Discussion

LCH is a rare malignancy, first described in 1893 by Hand, in association with plura [3]. The male to female ratio in LCH is 3.7:1 [4]. LCH can be a unisystem or a multisystem disorder; nevertheless, bone involvement predominates (80% of cases) with osteolytic and asymmetric lesions, most often of the skull. In the endocrine system, the pituitary is the most common site [5]. The involvement of the thyroid gland, even in the disseminated form of LCH is extremely rare. Literature review reveals less than 75 cases of thyroid involvement in LCH, the majority being a part of multisystem disease [1].

Clinical and radiologic diagnosis is relatively difficult, it can easily confused on clinical grounds with other popular entities such as undifferentiated carcinoma, lymphoma, lymphocytic thyroiditis, chronic granulomatous thyroiditis, and cystic degeneration of multinodular goiter. Initial steps in the diagnosis of primary thyroid LCH mainly based on USG and FNAB. On USG, diffuse involvement of the entire thyroid is seen in 59%, nodular enlargement in 25.8%, and irregular enlargement in 13.6% cases [6].

Although FNAB may be useful in the diagnosis for thyroid LCH, it has shown to be variable with some cases being misdiagnosed as “atypical follicular epithelial cells” and papillary or medullary carcinoma. Therefore, histology remains the most sensitive diagnostic modality, although there have been cases of histological misinterpretation of LCH interpreted as poorly differentiated carcinoma (Table 1). LCH

characterized by cytoplasmic rod shaped organelles (Birbeck granules) are a type of dendritic cell and are classed as antigen-presenting cells of the skin epidermis [1]. The cytologic features of LCH are characteristic, in particular, the eccentric nuclei with folded nuclear contours and linear nuclear grooves.

Table 1
Differential diagnosis of thyroid LCH

Disease	Morphology	Immunophenotype
LCH	Grooved nuclei, eosinophils	CD1a+, S100+, CD207+
PTC	Papillary architecure, pseudoinclusions	TTF-1, Thyroglobulin+
Thyroid lymphoma	Monomorphic lymphoid cell	CD20+, PAX5+
Hashimoto thyroiditis	Hurthle cell, lymphoid follicles	CD1a-
Subacute thyroiditis	Granulomas, giant cells	CD1a-

Immunohistochemical studies are extremely beneficial in confirming the histologic impression because LCH are positive for S100 protein and CD1a, and both markers can be used to assess formalin-fixed, paraffin-embedded tissue sections (Table 1). Electron microscopy is also helpful by allowing identification of the pathognomonic Birbeck granules but not essential for diagnosis. At a molecular level, LCH express CD1a, langerin (CD207), and S100 protein, but do not express markers which are possessed by mature dendritic cells such as CD83. Two inflammatory conditions to be considered in the differential diagnosis of LCH involving the thyroid gland are subacute granulomatous thyroiditis and chronic lymphocytic thyroiditis. The presence of eosinophil -rich infiltrate is extremely helpful for the correct diagnosis of LCH as well as excluding a primary thyroid carcinoma. The presence of giant cells and associated fibrosis in LCH may lead to an erroneous diagnosis of subacute granulomatous thyroiditis. The presence of numerous lymphocytes may lead to the misdiagnosis of chronic lymphocytic thyroiditis (Table 1).

Table 2
Literatures of thyroid LCH cases

Authors	Year	Gender	Age (year)	Other organs involvement	Chief complaint	Treatment
Pandayaraj [7]	2014	M	45	NR	Thyroid nodule	Surgery
Xin Wu [8]	2017	M	40	Hypothalamus pituitary	Thyroid nodule	Surgery, C/T
Dursun A. [9]	2020	M	45	Nil	Neck swelling, pain	Surgery
Subhash C. [10]	2022	F	38	Hypothalamus pituitary	Neck swelling	Surgery
Jing-Jing Shi [11]	2023	F	26	Ln, bone	Thyroid nodule	C/T, steroid
Kenana Tawashi [12]	2023	F	21	bone	Tachycardia, fever, frontal tumor	antithyroid
Xiao Fen Li [13]	2023	F	47	LN, liver, pituitary gland, skin	Neck swelling	C/T, steroid
Our case	2026	F	35	NR	Thyroid nodule	Surgery, C/T

F female, *M* male, *LN* lymph node, *NR* not recorded, C/T chemotherapy.

Treatment and outcome of thyroid LCH depend upon the extent of disease and its progression. LCH disease has a worse prognosis than monofocal disease, with 10–30% mortality and a 50% risk of life-impairing morbidity. It is important to distinguish isolated thyroid LCH from multisystemic cases because single-organ involvement is associated with excellent survival, close to 100% [14]. So, elaborate imaging including computed tomography chest, MRI brain, abdominal USG, and bone scintigraphy are necessary to rule out disease elsewhere to decide the line of treatment. For disseminated disease, combination chemotherapy, steroids along with radiotherapy are recommended (Table 2).

This report has several limitations. First, we were unable to perform genetic mutation testing related to the disease, such as BRAF V600E which has significant implications for the diagnosis and treatment of this condition. Second, the follow-up period was relatively short, which limited our ability to fully evaluate the patient's post-treatment outcomes.

Conclusions

Thyroid LCH is an exceptionally rare entity that may clinically and cytologically mimic thyroid malignancy. Accurate diagnosis relies heavily on histopathological examination and immunohistochemistry,

particularly CD1a and S100 expression. Awareness of this rare differential diagnosis is essential to avoid diagnostic pitfalls and guide appropriate systemic evaluation.

Patient perspective

The patient provided consent for publication and considered that sharing this case could contribute to data about rare cases relating to this disease.

Abbreviations

LCH Langerhans cell histiocytosis

MAPK Mitogen-activated protein kinase

FNAB Fine needle aspiration biopsy

USG Ultrasonography

Declarations

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Author 's contributions

Van Nam Nguyen analyzed the data and wrote the first draft. Ngoc Trung Nguyen revised the article critically for important intellectual content. All authors substantially contributed to the conception and design of this article and gave final approval for the version for publication and agree to be accountable for all aspects of the work.

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Data availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation

Ethics approval and consent to participate

The study was approved by the Research Ethics Committee of Military Hospital 103, Military Medical University, Viet Nam and a written consent for publication was obtained from the patient.

Consent for publication

Written informed consent for publication of this case report and the accompanying images was obtained from the patient. A copy of the written consent is available for review by the Editor for this journal.

Competing interests

The authors declare no competing interests.

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Figures

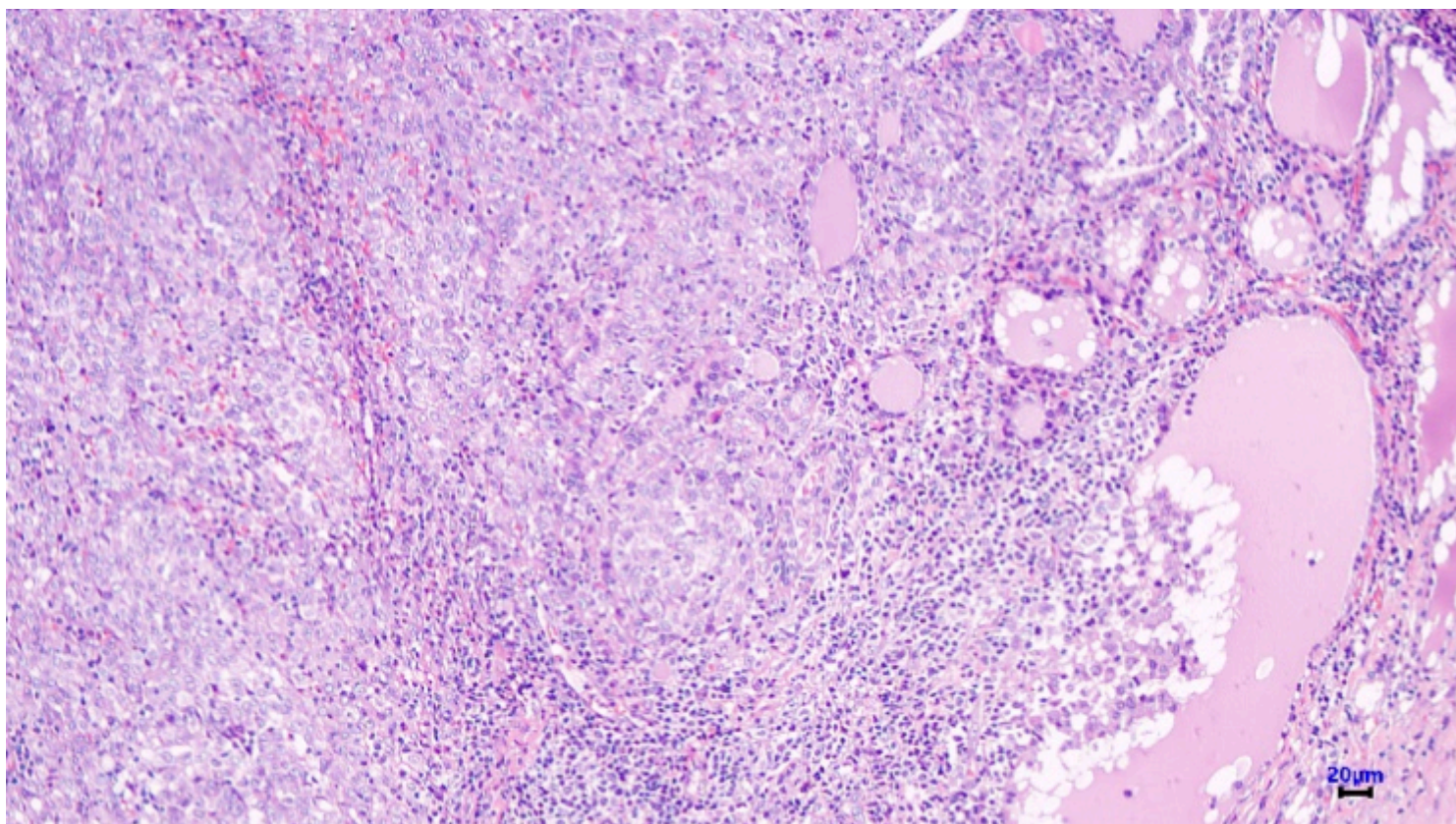


Figure 1

Diffuse infiltration of thyroid parenchyma by atypical histiocytic cells with associated eosinophilic infiltrates leading to destruction of thyroid follicles (H&E, ×100).

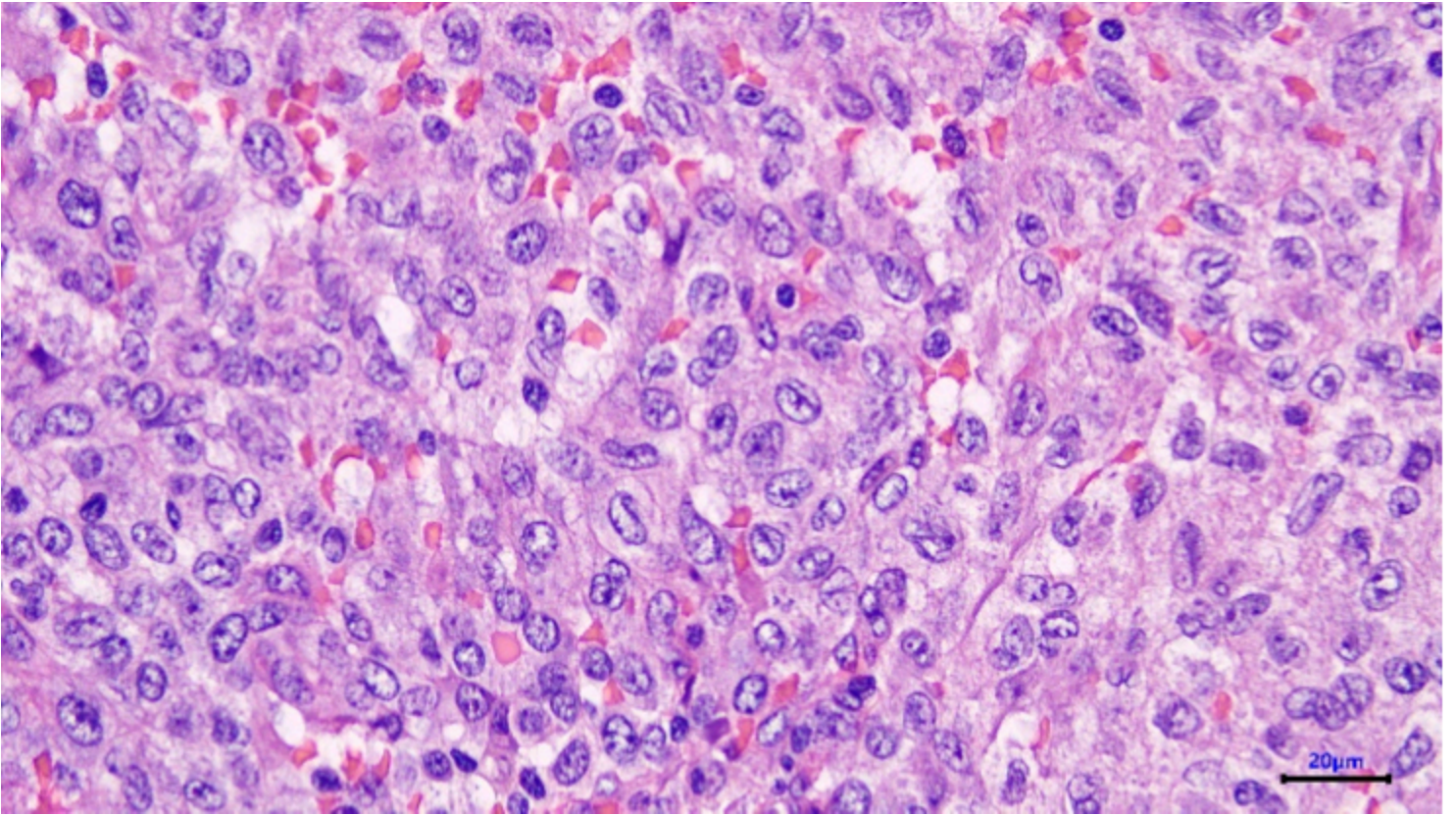


Figure 2

Large histiocytic cells showing characteristic grooved nuclei and eosinophilic cytoplasm (H&E, ×400).

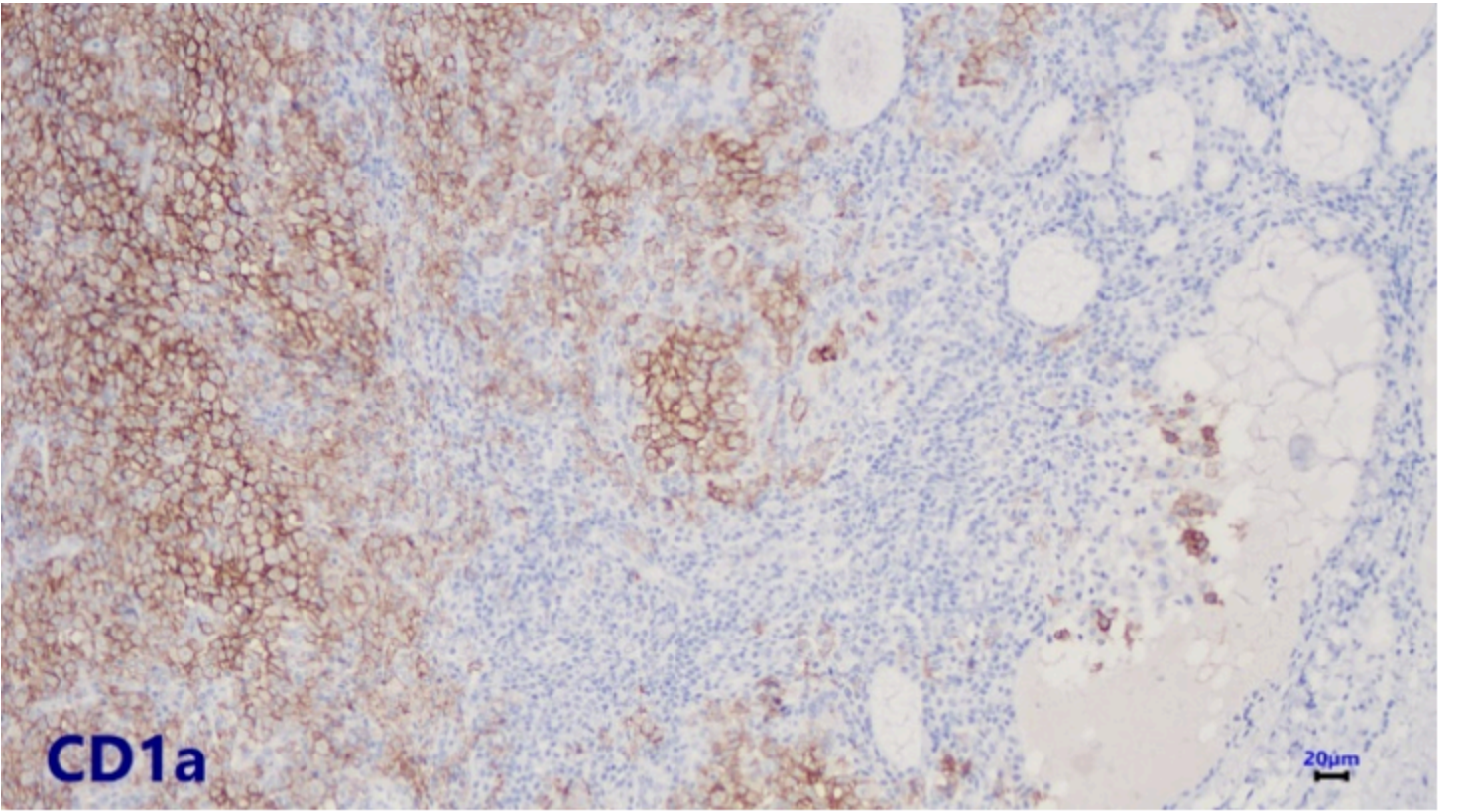


Figure 3

Tumor cells demonstrating diffuse membranous positivity for CD1a immunohistochemistry (x400)

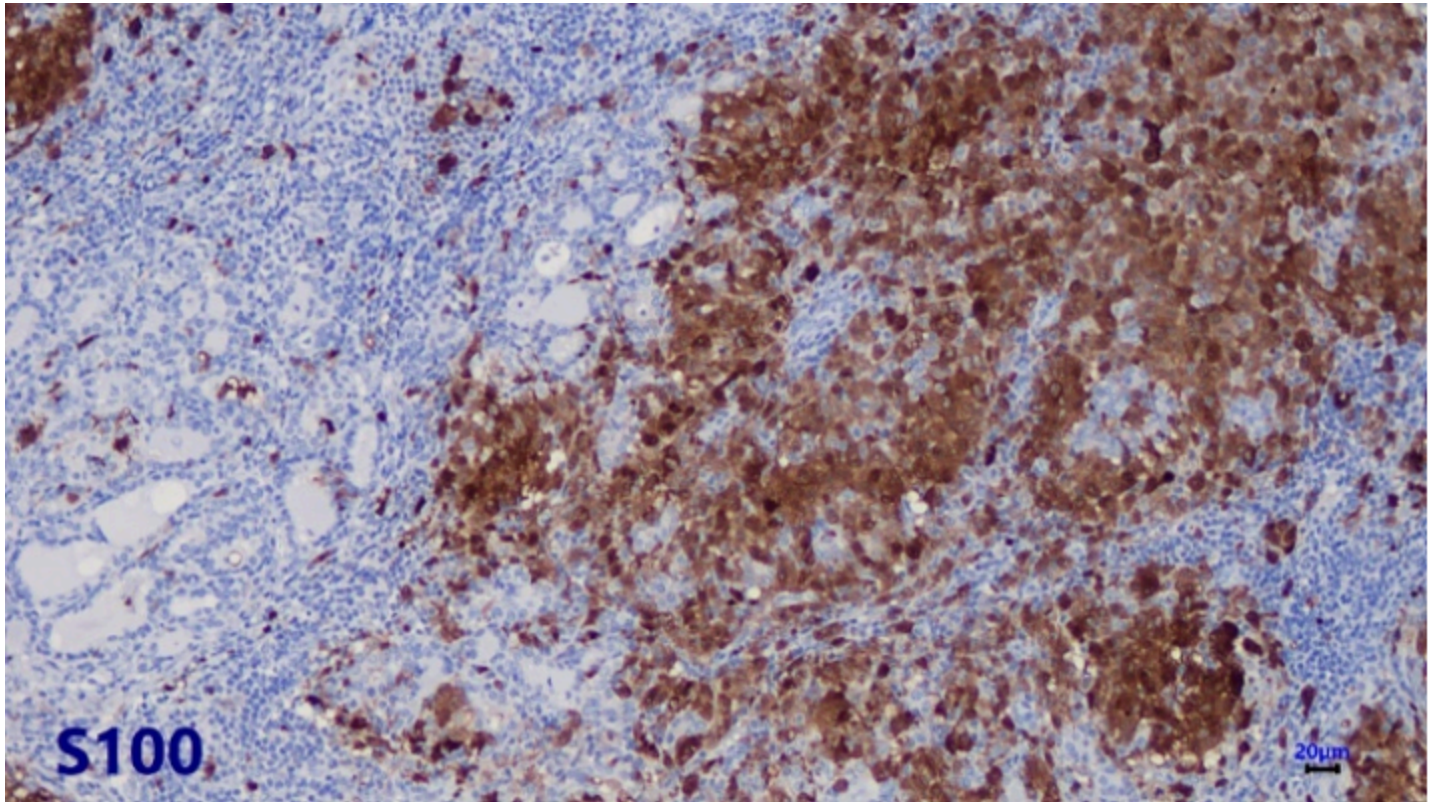


Figure 4

Strong nuclear and cytoplasmic immunoreactivity for S100 protein in lesional cell (x400)

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