Clinicopathological Features and Treatment of Thymic Lymphoepithelioma-Like Carcinoma: Two Case Reports and Literature Review

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Case Report

Keywords: thymic, lymphoepithelioma-like carcinoma, cytokeratin, immunohistochemical

Posted Date: September 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-77033/v1

Abstract

Background: Lymphoepithelioma-like carcinoma (LELC) is rare in the thymus, which is easy to be misdiagnosed. To improve its clinicopathological knowledge, we describe two cases of thymic LELC, and investigate their clinicopathological features (microscopical and immunohistochemical features), treatment and follow-up data with a review of previously published cases.

Case presentation: Two patients in the First Affiliated Hospital of China Medical University underwent complete surgical resection for thymic LELC. In both, they were treated with chemotherapy or radiotherapy after operation. Histologically, tumor cells were arranged in nest-like patterns or stripe-shaped infiltration in collagen fibrous interstitial tissue containing lymphocytes. And the tumor cells were diffusely positive for broad spectrum pan-cytokeratin (CK), CK19, CD5, CD117, epithelial membrane antigen (EMA) and p63, focally positive for CD20, and negative for TdT. Recent clinical reexamine showed that the two patients were alive with no signs of recurrence.

Conclusion: We report two cases of thymic LELC with a review of previously published cases to summarize the knowledge of their clinicopathological characteristics, which is necessary for the accurate diagnosis and clinical treatment.

Background

As a malignant tumor, lymphoepithelioma-like carcinoma (LELC) has been reported from a variety of organs, including lung, skin and nasopharynx. However, it is very rare in thymus, which is recognized in the second edition of the World Health Organization (WHO) classification of thymic tumors (2004). Thymic LELC is a high grade neoplasm with aggressive features and frequent metastasis [1]. This tumor has the capacity of metastasis to other organs, including liver, lung and bone, and the prognosis is generally poor [2, 3]. However, this tumor may be misdiagnosed if the pathologist is not familiar with its clinicopathological features. To improve the pathological knowledge of this tumor, we present two cases of thymic LELC in the First Affiliated Hospital of China Medical University, and investigate the clinicopathological features and its prognosis with a review of previously published cases.

Case Presentation

Case 1

This patient is a 64-year-old woman. She presented with vertigo for one month. Occasionally, her chest felt rather tight with shortness of breath and blurred vision. This patient had been weak lately, but her diet and sleep were normal.

The computed tomography (CT) scan showed that the chest was symmetrical and there was cord-like shadow in both lungs. Pulmonary micronodular lesions were detected in the upper lobe of the left lung; calcification could be seen in lower lobe of the left lung. There was a lobulated mass in the anterior

mediastinum measuring 1.9 × 2.3 cm. The boundary was not clear, but no mediastinal lymphadenectasis. CT attenuation values were 57 Hounsfield units (HU). After enhanced scanning, CT attenuation values were 63 HU (**Fig**. 1a, b). The detection of 18F fluorodexyglycose positron emission tomography/CT (FDG-PET/CT) showed that there was no abnormal accumulation to indicate distant metastasis. A tumor 1.5 × 2.1 cm in size was completely resected. The postoperative pathology was diagnosed as thymic LELC.

Histologically, tumor cells were arranged in nest-like patterns or stripe-shaped infiltration in collagen fibrous interstitial tissue containing lymphocytes (**Fig**. 1c, d). The tumor cells had large vacuolated nuclei and irregular chromatin. Cell boundary was not distinctive, and the nucleus was crowded or overlapped. We can see the mitosis in nucleus (**Fig**. 1e, f).

Immunohistochemically, the tumor cells were diffusely positive for pan-CK (Cytokeratin AE1 + AE3), CK19 and EMA, as well as CD5 and CD117, while infiltrated B lymphocytes were positive for CD20. Positive nuclear expression of p63 was detected in the tumor cells. Ki67 index was about 20%. TdT was negative in tumor cells, as well as lymphocytes around tumor cells (**Fig. 2**). Above all, pathological diagnosis was thymic LELC.

The patient was treated with a chemotherapy regimen as following: Docetaxel (140 mg/m2, day 1) and carboplatin (500 mg/m2, day 1) every for four cycles, each lasting twenty days. At the same time, liver protection treatment was carried out. A subsequent clinical examination showed that there was no sign of tumor recurrence. After 3 years of follow-up, the patient was alive without tumor recurrence or metastasis.

Case 2

A 52-year-old male patient had the symptom of cough for four months and continued to worsen. Chest CT revealed an abnormal shadow. He came to our hospital and chest CT results showed a soft tissue density mass in the anterior mediastinum, measuring 9.55 × 4.86 × 5.3 cm. The boundary between the lesion and pericardium was not clear. CT attenuation values were 43 HU (**Fig**. 3a, b)..

Cut the sternum into the chest and excised the mediastinal tumor. The operation lasted 85 min and bleeding was 40 ml, while the tumor size was 9 × 5 × 2.5 cm. And the boundary with thymus tissue is not clear.

Postoperative pathology showed that the tumor cells were nests or cords, which was divided by fibrous septum and dense lymphocytes. The nuclei of tumor cells were empty and bright or hyperchromatic (**Fig**. 3c, d).

Immunohistochemical analysis revealed tumor cells were diffusely positive for pan-CK, CK19, CD5, CD117, EMA and p63, focally positive for CD20, and negative for TdT. Ki67 index was about 60% (**Fig**. 4). The detection of EB-encoded RNA in situ hybridization for the tumor was negative . Above all, pathological diagnosis was thymic LELC.

The patient was treated with radiotherapy 20 days after operation. And then he was treated with a chemotherapy regimen 1 month after radiotherapy: Etoposide (100 mg/m2, day 1-5) and cisplatin (30 mg/m2, day 1-3) every for four cycles, each lasting three weeks. A subsequent clinical examination showed that there was no sign of tumor recurrence. After 2 years of follow-up, the patient was alive without tumor recurrence or metastasis.

Discussion And Conclusions

Lymphoepithelioma-like carcinoma is a rare subtype in thymic carcinoma, which is originally named by Snover et al [4]. The patients with thymic LELC almostly had chest pain and respiratory symptoms, but no pathological nerve reflex. Most of them experienced tumor recurrence or metastasis during the follow-up period. The survival time of these patients barely exceeded 1 year [5, 6]. We summarize the clinical data and prognosis of the reported cases [2, 3, 7-19] and ours (Table 1). We can find that the patients are dominated by adolescents and the elderly, and most patients with tumor metastasis have poor prognosis. Among the patients with reported prognosis, there were 11 patients with lymph-node metastasis and other distant metastasis. The surgical treatment was performed for 8 of 14 patients with reported prognosis. This indicated that surgery was necessary for thymic LELC patients with metastasis. The combination of operation with chemotherapy or radiotherapy is well for thymic LELC patients without metastasis.

Given the rarity of thymic LELC, we discuss the present case mainly by microscopical and immunohistochemical analysis, referring to the existing literatures of the previously reported cases. Thymic LELC belongs to the high-grade histology group, which has a series of histological features [14, 15, 20]. First of all, the tumor cells, looking like those in lymphoepithelioma of nasopharynx, gathered into interconnected or zigzag shape. They are scattered in collagen fibrous interstitial tissue. This feature is called “infiltrative growth”. In addition, the nucleus, with lobulated or round shape, contains a prominent eosinophilic nucleolus. This feature is called “heterotypic cell”. Besides, lymphocytic infiltration not only exists in interstitial area, but also mixes with tumor cells. Tumor cells are usually surrounded by lymphocytic infiltration. This feature is called “lymphocytic infiltration”. What's more, the necrotic area is often found. This feature is called “necrosis”. Finally, mitosis is very common. This feature is called “mitosis”. And there is a lack of intercellular bridge and keratinization.

We summarize the Immunohistochemical detection of the reported cases [12, 13, 21, 22, 23] and our case (Table 2). The tumor cells in these cases expressed different subtypes of CK. It is well known that low molecular weight of CK (CK-LMW) includes CK8, CK18, and CK19. They are positively expressed in glandular epithelium, as well as malignant tumors derived from glandular epithelium such as adenocarcinoma. It has been reported that thymic LELC is strongly positive for both p63 [21]. p63 is a marker of myoepithelial cell. It is mainly expressed in myoepithelial cells and squamous cells, as well as squamous cell carcinoma. The p63 positive expression confirms that there is squamous metaplasia [24, 25]. Expression and distribution of EMA is similar to that of CK. Joint detection of EMA and CK

expression is often used. So these cases expressing above protein factors, indicating that thymic LELC in these cases may have various malignant differentiation.

CD5 is a useful immunohistochemical staining for the diagnosis of thymic LELC. TTF-1 is commonly negative in thymic epithelial tumors [26]. Most of these cases have CD5 positive expression and TTF-1 negative expression. CD117 (c-kit) is almost positive in these cases. Nakagawa K et al confirmed that CD117 had positive immunoreactivity in thymic carcinomas, and joint detection of CD117 and CD5 is a effectIve way to distinguish between thymic carcinoma and lung carcinoma [27]. Ki67 index is commonly high in these cases, indicating that these cases have high grade malignancy.

The positive expressions of chromogranin A (CgA), neuron-specific enolase (NSE) and synaptophysin (SYN) indicated that the tumor had neuroendocrine activity. CD20 and CD99 expressions in all detected cases were hardly positive.

Thymic LELC is extremelly rare. For the diagnosis of thymic LELC, we should observe the arrangement of tumor cells and fibrous interstitial, marked nuclear atypia, and infiltrating lymphocytes by microscope. Then we could choose the immunohistochemical markers (CK8, CK18, CK19, p63, EMA, CD5, CD117 for positivity; CK20, CD99 and TdT for negativity) contrapuntally for diagnosis and differential diagnosis. We can get correct diagnosis by the representative microscopical features and pertinent immunohistochemical test. For the treatment of thymic LELC, surgery was necessary for all thymic LELC patients, and the combination of surgery with chemotherapy or radiotherapy is well for thymic LELC patients without metastasis.

To our knowledge, this is the first review of the clinicopathological features (histologic and immunohistochemical features) of previously reported thymic LELC, with the summarization of their treatment and prognosis. It provides an effective approach to improve the diagnosis and treatment of thymic LELC.

Abbreviations

LELC
lymphoepithelioma-like carcinoma; CT:computed tomography; HU:Hounsfield units; CK:cytokeratin; EMA:epithelial membrane antigen; TdT:terminal deoxynucleotidyl transferase; WHO:World Health Organization; IHC:immunohistochemistry; PBS:phosphate buffered saline.

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committees of the First Affiliated Hospital of China Medical University.

Consent for publication

Written consent for publication was obtained from the patient.

Availability of data and material

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by the National Natural Science Foundation of China (No. 81602022 to Huanyu Zhao, No.81171650 and 81672082 to Guangping Wu).

Authors' contributions

HZ, XG, EW and GW designed the study and analysed the data. HZ, XG and GW drafted the article or revised it critically for important intellectual content. HZ, DZ, YH, QL and GW evaluated the histopathological images and prepared the figures. All authors have reviewed and agreed to this submission of the final manuscript.

Acknowledgements

We thank Dr. Weinan Li for his technical support.

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Tables

Table 1
The information of thymic LELC cases reported in literature

Case	N	Age/Sex	Metastasis	Treatment	Follow-up
Ref [2], 1993	1	13/Female	LN	RE + RT + CT	Died (22 months)
Ref [3], 1990	2	19/Male	Neck, bone	RE + RT + CT RE + RT + CT	Died (39 months)
		41/Male	Lung, bone		Died (18 months)
Ref [7], 1988	2	28/NR	No	CT + RT	Died (28 months)
		43/NR			Died (36 months)
Ref [8], 1994	1	13/Female	No	CT + RT	Alive (12 months)
Ref [9], 1996	1	14/Male	No	RE + RT + CT	Alive (12 years)
Ref [10], 1998	1	65/Female	No	RE	Alive (6 months)
Ref [11], 2000	1	11/Male	LN	RE + RT + CT	Died (12 months)
Ref [12], 2001	2	59/Male	NR	NR	Alive (39 months)
Ref [13], 2004	2	65–75	Bone, LN, lung	RT + CT	Died (15 months)
		Male/Female		RE + RT	Died (39 months)
Ref [14], 2006	1	16/Female	Lung-bone	CT + RT	Died (15 months)
Ref [15], 2006	2	14/Male	Pleura	CT + RT	Died (10 months)
		10/Male	Lung	RE + CT + RT	Died (11 months)
Ref [16], 2007	1	10/Male	Vessel	CT + RE + RT	Alive (1 year)
Ref [17], 2008	1	16/Male	Pleura	RT + RE + CT	Died (11 months)
Ref [18], 2014	1	14/Male	Bone	CT	Died (10 months)
Ref [19], 2018	5	55/Male	No	RE	Alive (16 years)
		57/Female	No	RE	Alive (16 years)
		60/Male	No	RT	Alive (8 years)
		20/Male	No	No	Alive (7 years)
		67/Female	No	RT + CT	Died (1 month)

Case	N	Age/Sex	Metastasis	Treatment	Follow-up
Our case	2	64/Female	No	RE + CT	Alive (3 years)
		43/Female	No	RE + RT + CT	Alive (2 years)
N, number; NR, no record; LN, lymph nodes; CT, chemotherapy; RT, radiotherapy; RE, resection.					

Table 2 Immunohistochemical detection of tumor cells in thymic LELC cases

Marker	Ref [12]		Ref [13]		Ref [21]	Ref [22]	Ref [23]	Ours	
	No. 1	No. 2	No. 3	No. 4	No. 5-12	No. 13-15	No.16-19	No. 20	No. 21
CgA	ND	□	ND	ND	PC: 5	PC: 2; NC: 1	ND	ND	ND
SYN	ND	F□	ND	ND	PC: 7	PC: 1; NC: 2	ND	ND	ND
NSE	ND	ND	ND	ND	ND	PC: 2; NC: 1	ND	ND	ND
p63	ND	ND	ND	ND	All □	ND	ND	□	□
Ki67	high	high	ND	ND	10–70%	ND	ND	20%	60%
pan-CK	ND	ND	□	□	ND	ND	ND	□	□
CK8	ND	ND	ND	ND	ND	□	ND	ND	ND
CK18	ND	ND	ND	ND	ND	□	ND	ND	ND
CK19	ND	ND	ND	ND	ND	□	ND	□	□
CK20	ND	ND	ND	ND	ND	□	ND	F□	ND
CD5	□	□	□	□	PC: 5	ND	ND	□	□
CD20	L□	L□	ND	ND	ND	ND	ND	F□	F□
CD99	□	□	□	□	ND	ND	ND	ND	ND
CD117	ND	ND	ND	ND	PC: 7	ND	ND	□	□
TTF-1	ND	ND	ND	ND	All □	ND	ND	ND	ND
EMA	ND	ND	□	□	ND	ND	ND	□	□
TdT	ND	ND	ND	ND	ND	ND	ND	□	□
F□, focally positive; L□, positive expression in lymphocytes in the stroma; PC, positive case; NC,negative case; ND, no data.									

Figures

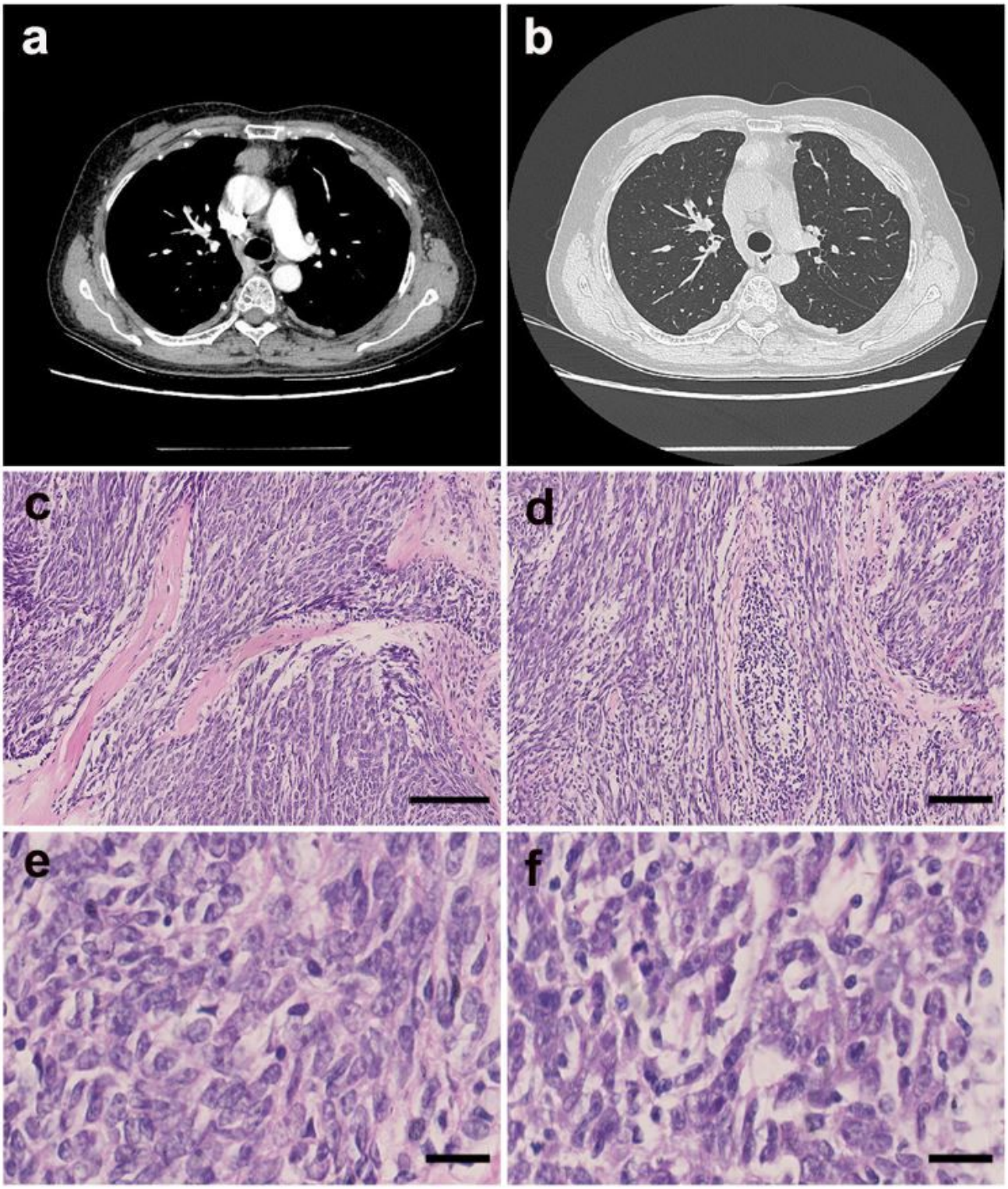

Figure 1

CT scan (a-b) and histological features (c-f) of thymic LELC. Bar = 400 μm (c-d); bar = 80 μm (e-f).

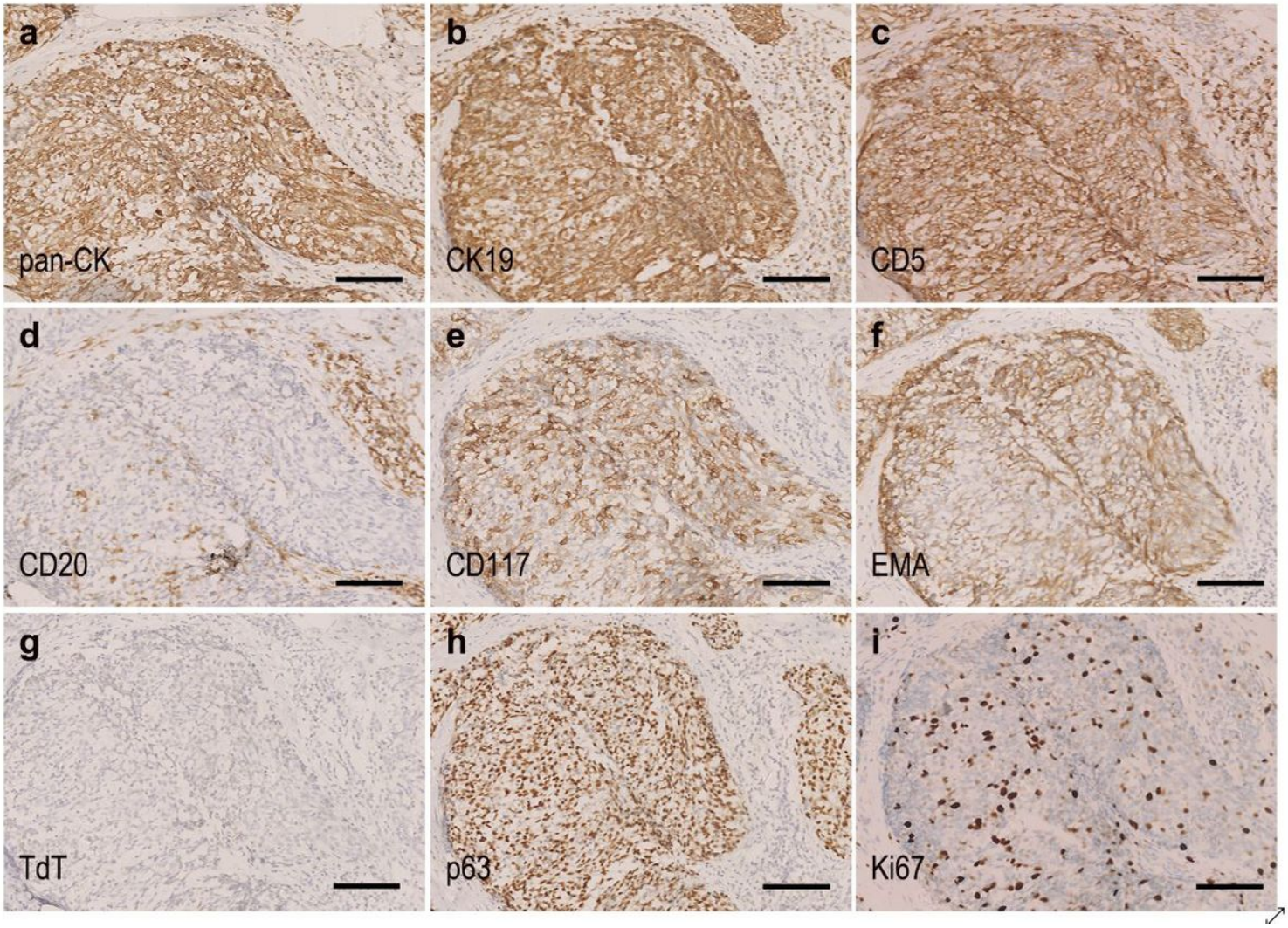

Figure 2

Immunohistochemistry examination of the tumor cells in thymic LELC. pan-CK (a), CK19 (b), CD5 (c), CD20 (d), CD117 (e), EMA (f), TdT (g), p63 (h), and Ki67 (i). Bar = 400 μm.

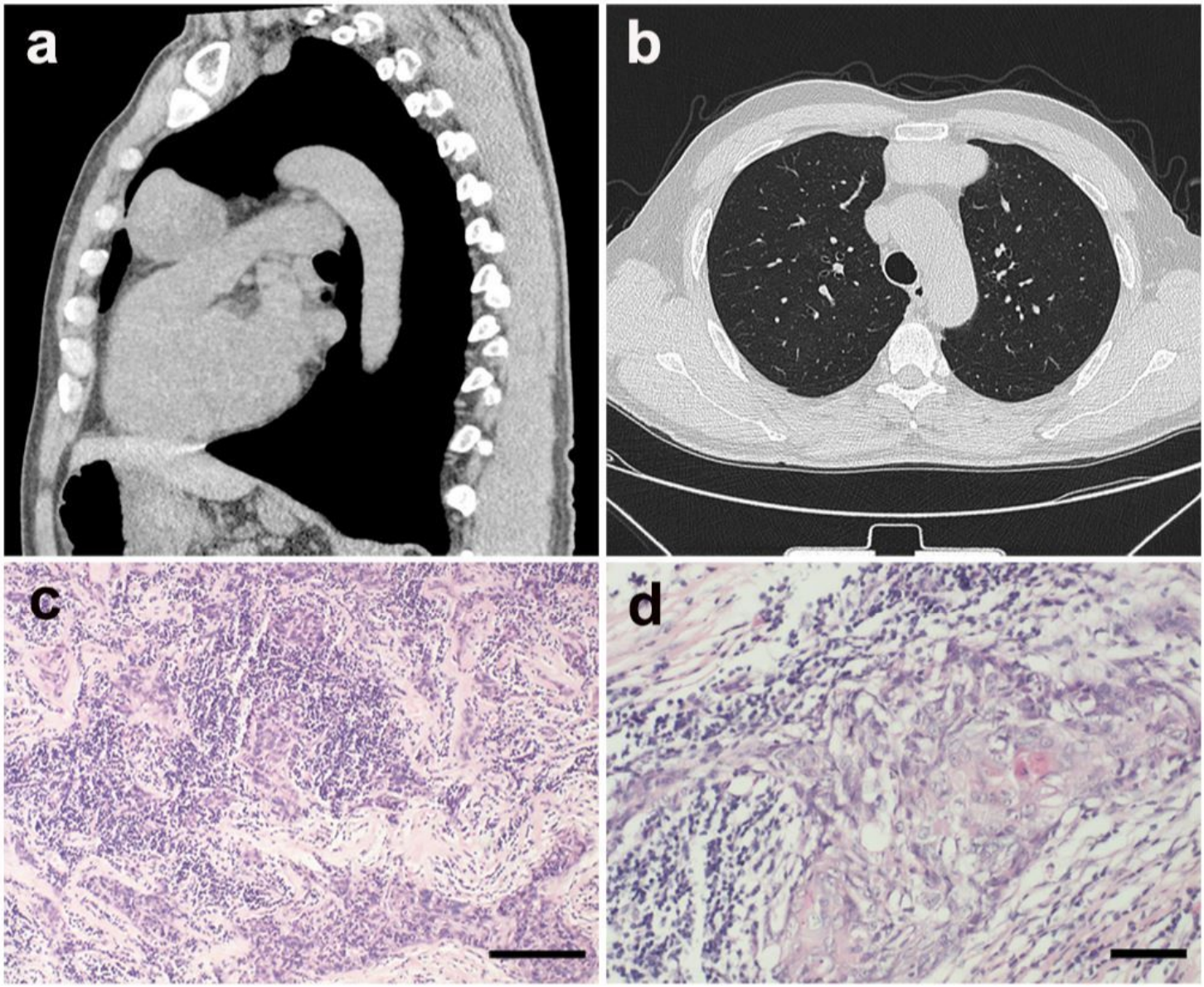

Figure 3

CT scan (a-b) and histological features (c-d) of thymic LELC. Bar = 400 μm (c); bar = 80 μm (d).

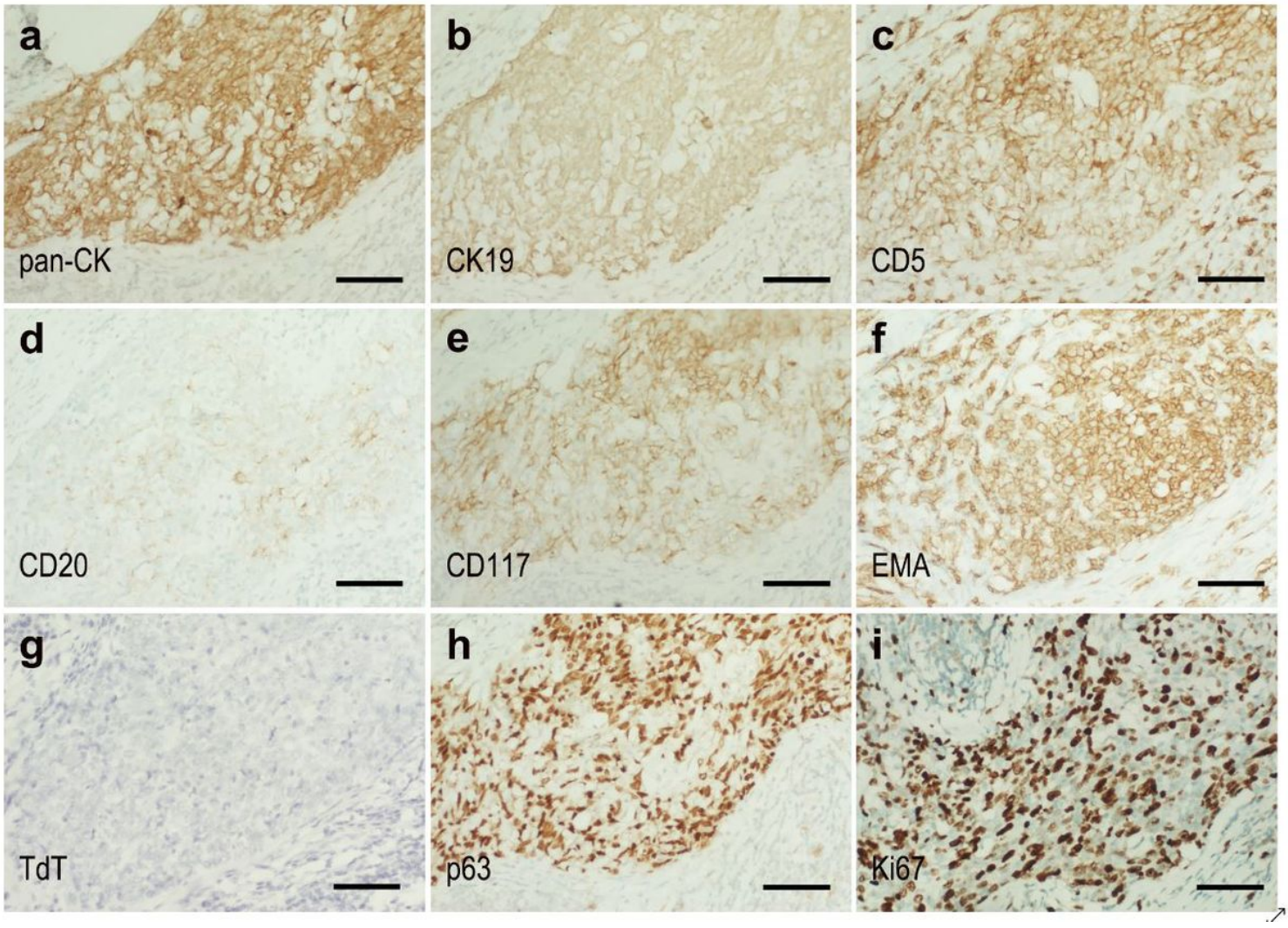

Figure 4

Immunohistochemistry examination of the tumor cells in thymic LELC. pan-CK (a), CK19 (b), CD5 (c), CD20 (d), CD117 (e), EMA (f), TdT (g), p63 (h), and Ki67 (i). Bar = 400 μm.

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