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Case Report

Clinicopathologic features and treatment of thymic lymphoepithelioma-like carcinoma: two case reports and literature review

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Abstract: Lymphoepithelioma-like carcinoma (LELC) is rare in the thymus, and easily misdiagnosed. To improve its clinicopathologic knowledge, we describe two cases of thymic LELC, and investigate their microscopic and immunohistochemical features, treatment, and follow-up with a review of previously published cases. Two patients in the First Affiliated Hospital of China Medical University underwent complete surgical resection for thymic LELC. They were treated with chemotherapy or radiotherapy after operation. Histologically, tumor cells exhibited nest patterns or showed stripe-shaped infiltration in fibrous tissue containing lymphocytes. Tumor was diffusely positive for pancytokeratin (CK), CK19, cluster of differentiation 5 (CD5), CD117, epithelial membrane antigen (EMA), and p63, and negative for TdT. Recent follow-up showed that the two patients were alive with no signs of recurrence. We report two cases of thymic LELC with a review of previously published cases to summarize knowledge of their clinicopathological characteristics, which is necessary for accurate diagnosis and clinical treatment.

Keywords: Thymic, lymphoepithelioma-like carcinoma, cytokeratin, immunohistochemistry

Introduction

Lymphoepithelioma-like carcinoma (LELC) has been reported in a variety of organs, including lung, skin, and nasopharynx. However, it is very rare in thymus, and 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 [1]. This tumor has the capacity to metastasize to other organs, including liver, lung, and bone, so that the prognosis is generally poor [2, 3]. At present, there are a variety of treatment methods for thymic LELC, including surgery, radiotherapy, and chemotherapy. If early stage patients receive surgical treatment as soon as possible, cure may be achieved, and the prognosis is good. Moreover, this tumor may be misdiagnosed if the pathologist is not familiar with its clinicopathologic features. Herein, we report two cases of thymic LELC in the First Affiliated Hospital of China Medical University with a review of previously published cases, including their clinicopathologic features, treatment and follow-up data.

Materials and methods

Tissues were fixed in 10% formalin and embedded in paraffin. Then we performed serial section (4 μm) to each paraffin block and used H&E and immunohistochemical (IHC) staining. Streptavidinperoxidase system (Ultrasensitive; Mai Xin, Fuzhou, China) was used for IHC staining. The tissues were stained with the following antibodies: broad-spectrum pan cytokeratin (CK), CK19, cluster of differentiation 5 (CD5), CD20, CD117, terminal deoxynucleotidyl transferase (TdT), epithelial membrane antigen (EMA), p63, and Ki67. We replaced the primary antibody with phosphate buffered saline (PBS) for the negative control. This study was approved by the Institute Research Ethics Committee at the First Affiliated Hospital of China Medical University. Written informed consent was obtained from the patient for publica-

tion of this case report and accompanying images.

Case presentation

Case 1

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

Computed tomography (CT) scan showed that the chest was symmetrical and there was a 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 (**Figure 1A**, **1B**). 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. It was diagnosed as thymic LELC.

Histologically, tumor cells exhibited nest patterns or showed stripe-shaped infiltration in fibrous tissue containing lymphocytes (**Figure 1C**, **1D**). The tumor cells had large vacuolated nuclei and irregular chromatin. Cell boundaries were indistinct, and the nuclei were crowded or overlapping. Mitotic figures were noted (**Figure 1E**, **1F**).

Immunohistochemically, the tumor cells were diffusely positive for pan-CK (Cytokeratin AE1 + AE3), CK19, 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 (**Figure 2**). Pathologic diagnosis was thymic LELC.

The patient was treated with a chemotherapy regimen: Docetaxel (140 mg/m^2, day 1) and carboplatin (500 mg/m^2, day 1) 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 symptoms of cough for four months and the condition continued to worsen. He came to the 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 (**Figure 3A**, **3B**).

The surgeons cut the sternum into the chest and excised the mediastinal tumor. The operation lasted 85 min and bleeding was 40 ml, and the tumor size was 9 × 5 × 2.5 cm.

Postoperative pathology showed that the tumor cells were in nests or cords, mixed with fibrous septum and dense lymphocytes. The nuclei were empty and bright or hyperchromatic (**Figure 3C**, **3D**).

Immunohistochemical analysis revealed tumor cells were diffusely positive for pan-CK, CK19, CD5, CD117, EMA and p63, and negative for CD20 and TdT. Ki67 index was about 60% (**Figure 4**). Detection of EB-encoded RNA in situ hybridization for the tumor was negative. Diagnosis was thymic LELC.

The patient was treated with radiotherapy 20 days after operation. He was then treated with a chemotherapy regimen 1 month after radiotherapy: etoposide (100 mg/m^2, day 1-5) and cisplatin (30 mg/m^2, day 1-3) 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

Background on thymic LELC

Thymic LELC is a rare subtype in thymic carcinoma. Patients with thymic LELC mostly had chest pain and respiratory symptoms, but no pathologic nerve reflex. Most of them experienced tumor recurrence or metastasis during

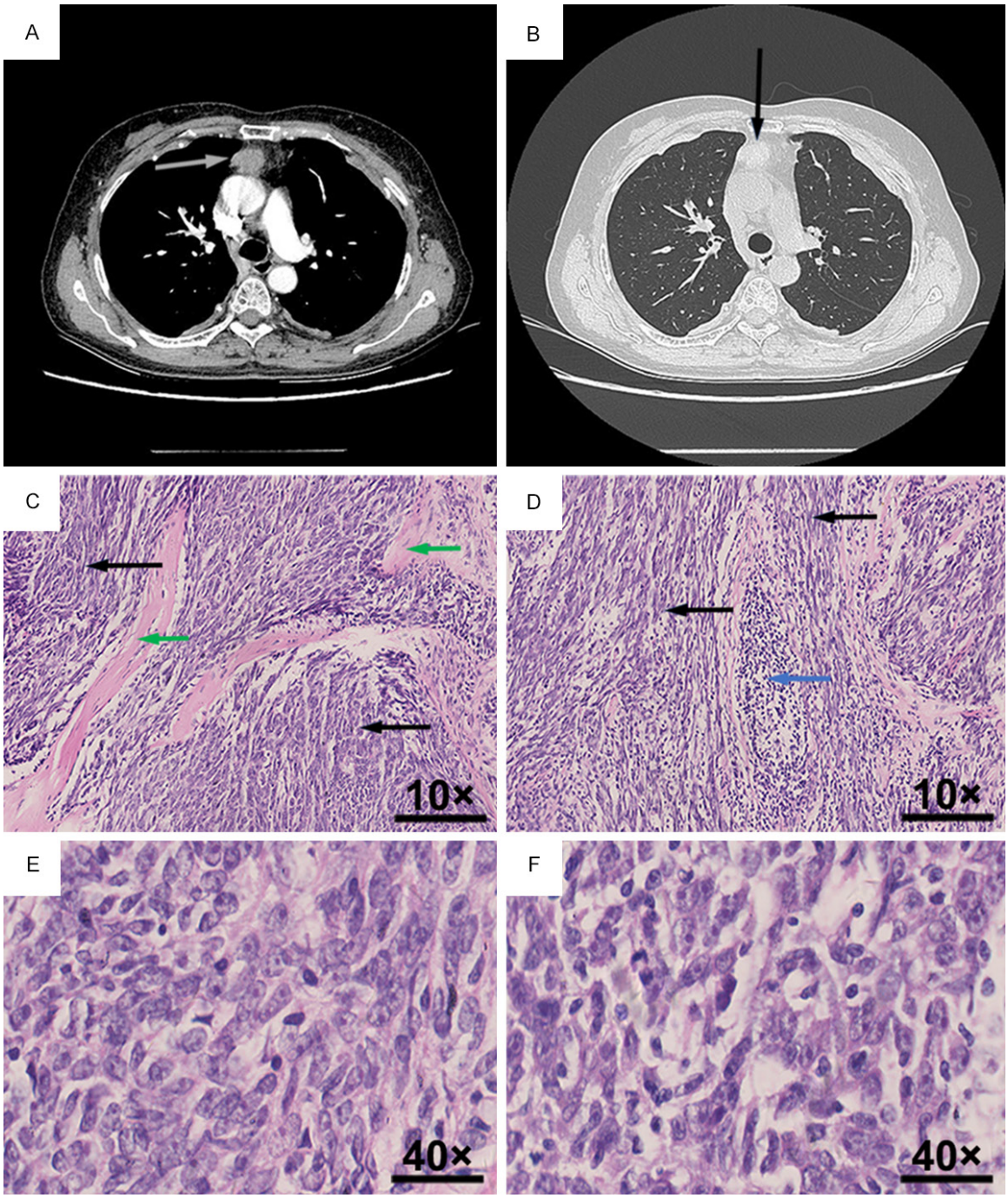

Figure 1. CT scan (A, B) and histologic features (C, F) of thymic LELC. A, B. The arrow points to the lesion; C, D. (H&E stain, 10×), black arrow points to tumor cells, green arrow points to fibrous tissue, and blue arrow points to lymphocytes; E, F. (H&E stain, 40×).

the follow-up period. The survival time of these patients barely exceeded 1 year [4]. We summarize the clinical data and prognosis of the reported cases [2, 3, 5-17] and ours (**Table 1**). Patients were mostly adolescents and the elderly, and most patients with tumor metastasis had a poor prognosis. Among the patients with reported outcome, 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 neces-

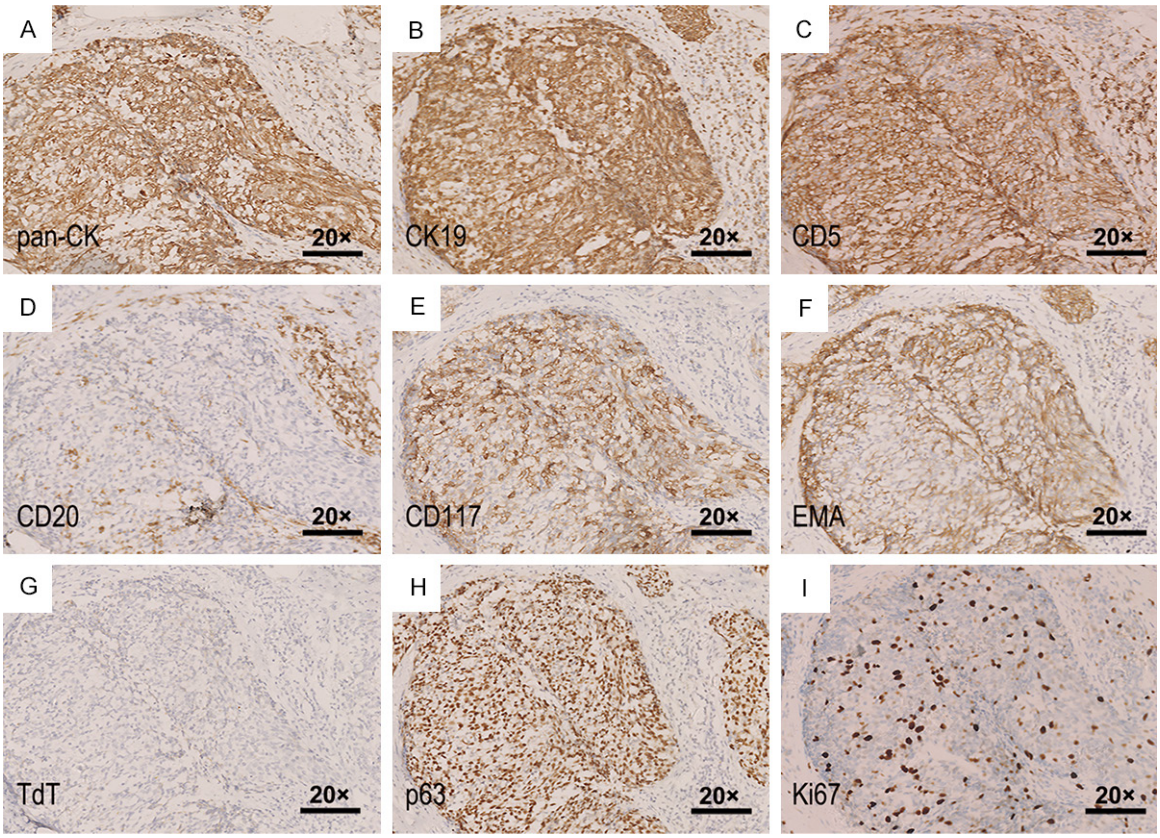

Figure 2. Immunohistochemical examination of the tumor cells in thymic LELC. pan-CK (A), CK19 (B), CD5 (C), CD20 (D), CD117 (E), EMA (F), TdT (G), p63 (H), and Ki67 (I) (A-I, 20×).

sary for thymic LELC patients with metastasis. The combination of operation with chemotherapy or radiotherapy is best for thymic LELC patients without metastasis.

Histopathologic features of thymic LELC

Given the rarity of thymic LELC, we discuss the present case with microscopic and immunohistochemical analysis, referring to previously reported cases. Thymic LELC belongs to the high-grade histology group, which has a series of histologic features [12, 13]. First of all, the tumor cells look like those in lymphoepithelioma of nasopharynx, gathered into interconnected or zigzag shape. They are scattered in fibrous tissue. This feature is called “infiltrative growth”. In addition, the nucleus, has a lobulated or round shape, and contains a prominent eosinophilic nucleolus. This feature is called “heterotypic cells”. Lymphocytic infiltration not only exists in the interstitial area, but also mixes with tumor cells. Tumor cells are usually surrounded by lymphocytic infiltration. Areas of necrosis are often found. Finally, cell mitosis is very common. There is a lack of intercellular bridges and keratinization.

Immunohistochemical features of thymic LELC

We summarize the Immunohistochemical findings in the reported cases [10, 11, 18-20] and our cases (**Table 2**). The tumor cells in these cases expressed different subtypes of CK. Low molecular weight of CK (CK-LMW) includes CK8, CK18, and CK19. They are positively expressed in glandular epithelium and malignant tumors derived from glandular epithelium. It has been reported that thymic LELC is strongly positive for p63 [18]. p63 is a marker of myoepithelial cells. It is mainly expressed in myoepithelial cells and squamous cells, as well as squamous cell carcinoma. p63 positive expression confirms that there is squamous metaplasia [21, 22]. Expression and distribution of EMA is similar to that of CK. Joint detection of EMA and CK expression is often used for thymic LELC. Expression of the above protein factors indicates that thymic LELC in these

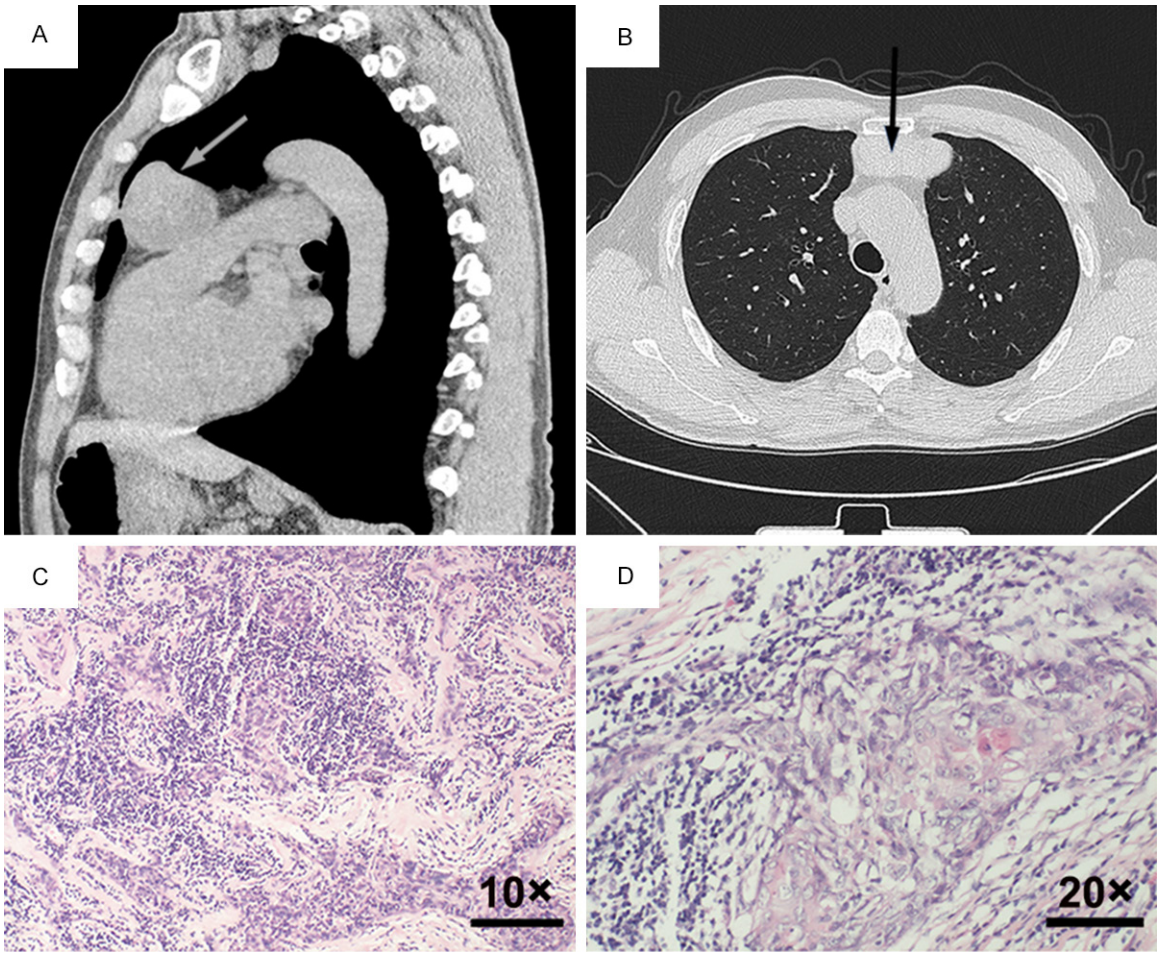

Figure 3. CT scan (A, B) and histologic features (C, D: H&E stain; C, 10×; D, 20×) of thymic LELC. A, B. The arrow points to the lesion.

cases may have various malignant differentiations.

CD5 is a useful immunohistochemical stai for the diagnosis of thymic LELC. TTF-1 is commonly negative in thymic epithelial tumors [23]. Most of these cases have CD5 positive expression and TTF-1 negative expression. CD117 (c-kit) is almost positive in these cases. Nakagawa et al confirmed that CD117 had positive immunoreactivity in thymic carcinomas. Joint detection of CD117 and CD5 is an effective way to distinguish between thymic carcinoma and lung carcinoma [24]. Ki67 index is commonly high in these cases, indicating that these cases have high malignancy.

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

Thymic LELC is extremely rare. For the diagnosis of thymic LELC, we should observe an arrangement of tumor cells and fibrous tissue, marked nuclear atypia, and infiltrated lymphocytes. Expected positiveimmunohistochemical markers are CK8, CK18, CK19, p63, EMA, CD5, CD117; CK20, CD99 and TdT should be negative, for diagnosis and differential diagnosis. We can get a correct diagnosis by the microscopic features and immunohistochemical tests. For the treatment of thymic LELC, surgery was necessary for all thymic LELC patients, and the combination of surgery with chemotherapy or radiotherapy is best for thymic LELC patients without metastasis.

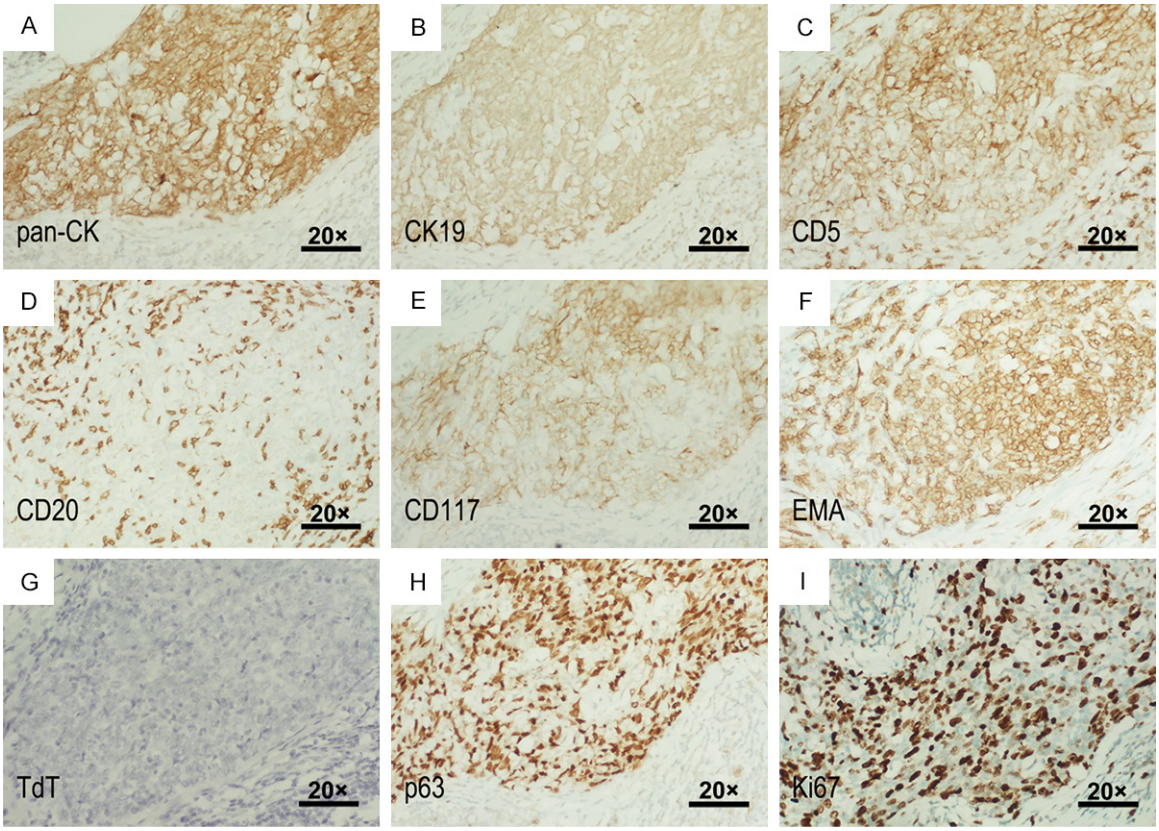

Figure 4. Immunohistochemical examination of the tumor cells in thymic LELC. pan-CK (A), CK19 (B), CD5 (C), CD20 (D), CD117 (E), EMA (F), TdT (G), p63 (H), and Ki67 (I) (A-I, 20×).

Table 1. 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	Died (39 months)
		41/Male	Lung, bone	RE+RT+CT	Died (18 months)
Ref [5], 1988	2	28/NR	No	CT+RT	Died (28 months)
		43/NR			Died (36 months)
Ref [6], 1994	1	13/Female	No	CT+RT	Alive (12 months)
Ref [7], 1996	1	14/Male	No	RE+RT+CT	Alive (12 years)
Ref [8], 1998	1	65/Female	No	RE	Alive (6 months)
Ref [9], 2000	1	11/Male	LN	RE+RT+CT	Died (12 months)
Ref [10], 2001	2	59/Male	NR	NR	Alive (39 months)
Ref [11], 2004	2	65-75	Bone, LN, lung	RT+CT	Died (15 months)
		Male/Female		RE+RT	Died (39 months)
Ref [12], 2006	1	16/Female	Lung-bone	CT+RT	Died (15 months)
Ref [13], 2006	2	14/Male	Pleura	CT+RT	Died (10 months)
		10/Male	Lung	RE+CT+RT	Died (11 months)
Ref [14], 2007	1	10/Male	Vessel	CT+RE+RT	Alive (1 year)
Ref [15], 2008	1	16/Male	Pleura	RT+RE+CT	Died (11 months)
Ref [16], 2014	1	14/Male	Bone	CT	Died (10 months)
Ref [17], 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)
Our cases	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 [10]		Ref [11]		Ref [18]	Ref [19]	Ref [20]	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	L+	L+
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.

Conclusion

To our knowledge, this is the first review of the clinicopathologic 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.

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Disclosure of conflict of interest

None.

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