

Original Article

Ectopic thymoma: report of 2 cases and review of the literature

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Received September 27, 2019; Accepted November 26, 2019; Epub December 1, 2019; Published December 15, 2019

Abstract: In this report, we present two cases of ectopic thymoma, aiming to explore the clinicopathologic features, diagnosis, and differential diagnosis of ectopic thymoma. Case 1 was a female 56-years-old. For 6 months' time, there was no obvious cause of cough, expectoration, chest tightness, or asthma with chest pain. PET-CT showed a right middle lung and lower lung mass with increased FDG metabolism. Postoperative pathology was diagnosed as right middle and lower lung ectopic thymoma, type B2, invading the chest wall. Case 2 was a male of 54-years-old. By physical examination the right chest cavity had a mass present for 1 week and he was admitted to hospital. Postoperative pathology was diagnosed as right thoracic ectopic thymoma, type AB. No recurrence has been found to in the follow-up of these two patients. In conclusion, ectopic thymoma occurs outside the anterior mediastinum. It is rare, the clinical symptoms are not typical, and pre-operative diagnosis is difficult. It is easily misdiagnosed as other diseases. Surgical treatment is the best method. According to the pathologic type and invasion of the tumor, radiotherapy may be considered.

Keywords: Ectopic thymoma, diagnosis, differential diagnosis, treatment

Introduction

Ectopic thymus is the result of a migration failure during development [1]. Thymoma often occurs in the anterior mediastinum, but may rarely be ectopic, and ectopic thymoma accounts for only 4% of all thymomas [2, 3]. The clinical symptoms of most ectopic thymomas are atypical, so clinical diagnosis is difficult and misdiagnosis occurs. Surgical resection is the main treatment [4, 5]. Below we report 2 cases of ectopic thymoma diagnosed in our hospital in recent years and review related literature, which helps us to better understand it and improve the diagnostic accuracy.

Materials and methods

Clinical information

First case: A female patient, 56 years old, was admitted to the hospital in 2017 due to "cough, expectoration, chest tightness and asthma with chest pain without obvious cause, starting

six months ago". Chest + head CT scan showed right lung lobe and lower lobe had a dense soft tissue mass, concerning for lung cancer. PET-CT showed: 1. Right lung and lower lung mass with increased FDG metabolism, suggesting a high metabolic site biopsy. 2. Right pleural effusion. 3. Right pleural thickening, with increased FDG metabolism. The operation performed was "Right thoracotomy, right lower middle lung lobe resection", and the lesion was located in the middle and lower lobe of the right lung, invading the right upper lobe, the diaphragm muscle, and pericardium and the parietal pleura. Furthermore the pericardial phrenic nerve was encased by tumor. We carefully separated the adhesions, and after the tumor collapsed, more grayish white fish meat was discharged with bloody liquid. Re-exploration revealed that the tumor was huge, invading the pericardium and the right upper lobe. It was difficult to remove the tumor from the right middle and lower lung lobes, so we performed intrapericardial treatment of pulmonary vascular right lung

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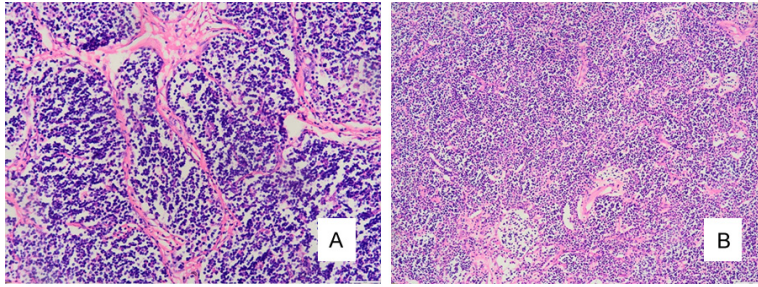


Figure 1. A. The leaflets are clearly structured and separated by acellular fibrous bands (H&E staining $\times 400$). B. The tumor cells are vacuolated and the nucleoli are more obvious. The interstitial is rich in lymphocytes (H&E staining $\times 400$).

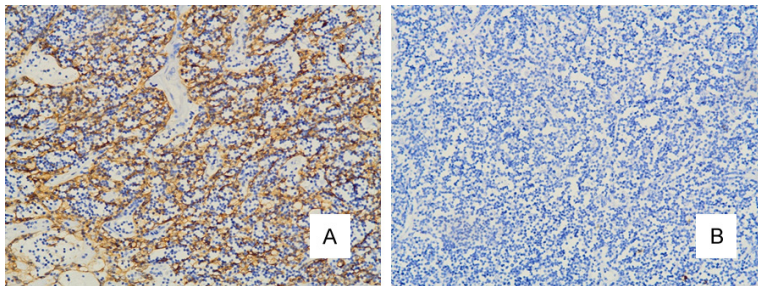


Figure 2. Immunohistochemical features of the tumor. A. Antibody expression of CK19 is positive (magnification, $\times 400$). B. Antibody expression of CD20 is negative (magnification, $\times 400$).

resection and a hilar mediastinal lymph node dissection.

Second case: A patient, male, 54 years old, was admitted to the hospital in 2011 due to “1 week of right thoracic space occupation found by physical examination”. During the course of the disease, there was no significant change in the patient’s body weight. X-ray and CT showed the right chest cavity had a mass, about 7 cm $\times$ 9 cm, considered teratoma or thymoma. Transthoracic tumor resection was performed, taking the right fifth intercostal anterior lateral incision layer by layer into the chest. The tumor was found in the right thoracic cavity, about 15 cm $\times$ 13 cm $\times$ 12 cm, and the capsule was intact.

Immunohistochemistry

Immunohistochemistry was performed according to the Elivision Plus detection kit instructions (Lab Vision, USA). Briefly, all control tissues were fixed in 10% buffered formalin and embedded in paraffin. The paraffin specimen was sliced in a series of 4 μ m thickness and baked. All sections were deparaffinized and dehydrated by xylene, and washed with differ-

ent concentrations of ethanol and PBS for 10 minutes (pH 7.2). Endogenous peroxidase activity was incubated in methanol containing 3% hydrogen peroxide for 10 minutes at room temperature (RT) and then subjected to antigen retrieval in citrate buffer (pH 6.0). All the slides were counterstained, dehydrated, air-dried and fixed using hematoxylin. The negative control group received omission of the original antibody during the staining process. Positive staining for ALDH1 and MACC1 was predominantly located in the cytoplasm of cancer cells.

Results

Gross

Case 1: A nodular mass, 10 cm $\times$ 10 cm $\times$ 6 cm, gray and grey red, within necrosis and cystic change.

Case 2: A grayish-red nodular mass, 15 cm $\times$ 10 cm $\times$ 6 cm. The capsule is complete and the cut surface is gray and soft. The sections are multinodular.

Microscopic examination

Case 1: The lobular structure was clear under the microscope and they were separated by acellular fibrous bands (**Figure 1A**). The tumor cells are vacuolated and the nucleoli are more obvious. Interstitium is rich in lymphocytes (**Figure 1B**), the tumor does not express CD20, and is CK19 positive. Case 2 also had a clear lobular structure under the microscope. Microscopically, a region lacking lymphocytes, which is a fusiform and oval epithelial cell, that is, a type A component (**Figure 3A**), could also be seen under the microscope. B-type tumor cells are composed of small polygonal epithelial cells with small nuclei and unclear nucleoli (**Figure 3B**). Lymphocytes are mostly TdT-positive T cells, while the type A component was negative for TdT. CD20-positive tumor cells were observed in both the A-type region and the B-type region.

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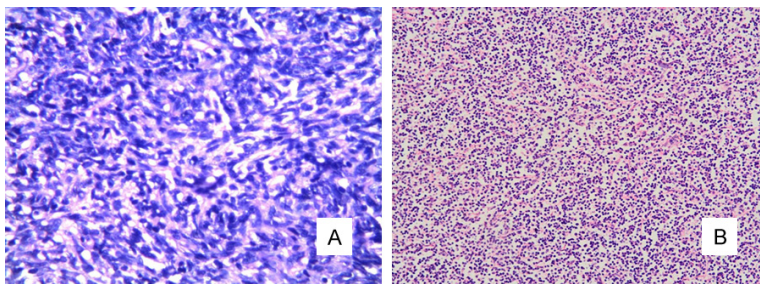


Figure 3. A. Type A component (H&E staining $\times 400$). B. Type B component (H&E staining $\times 400$).

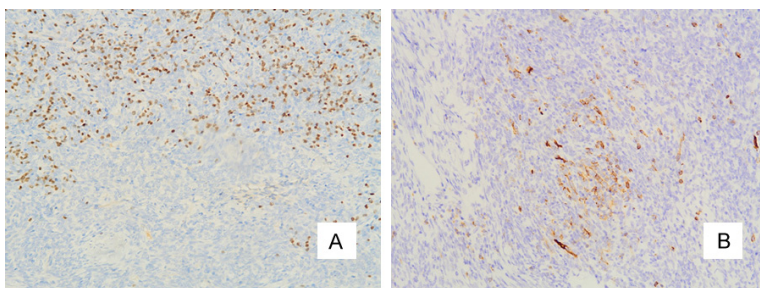


Figure 4. A. Type B component (top) lymphocytes in which TdT is mostly positive; type A component (bottom) is negative (magnification, $\times 400$). B. Antibody expression of CD20 is positive (magnification, $\times 400$).

Immunohistochemical features

Immunohistochemical expression results of the first patient: CD20 (-) (**Figure 2B**), P53 (2+), CK19 (2+) (**Figure 2A**), CD3 (+), CD43 (+), CD5 (+), TdT (+), CD99 (+), CD1a (+), CD7 (+), CD21 (-), CD35 (-), CD10 microfocal positive, pax-5 (-), CD117 (-), CD34 (-), napsinA (-), Ki-67 (3+, about 70%). Immunohistochemical expression results of the second patient: TdT lymphocyte (+) (**Figure 4A**), CD117 (-), CK19 (+), CD1 α lymphocyte (+), CD5 lymphocyte (+), P53 (-), Partially positive for CD20 (**Figure 4B**), EMA spindle cell (+), Ki-67 (+) <5%.

Pathologic diagnosis

The pathologic diagnosis of patient #1 was right middle and lower lung ectopic thymoma, type B2, invading the chest wall. There was no recurrence during postoperative follow-up. The pathologic diagnosis of patient #2 was right thoracic ectopic thymoma, type AB. Again, there was no recurrence after the operation.

Review of literature on ectopic thymoma

Review of the previous CNKI database, and Pubmed database literature showed a total of

114 cases of ectopic thymoma. The clinical information is summarized in **Table 1**. Among the 114 cases, 46 were male and 68 were female, with an average age of 53.1 years. The youngest patient was only 8 years old and the oldest was 83 years old. The maximum diameter of the mass varied from 18.0 cm to 0.3 cm. The shape of the mass could be round, round, elliptical, irregular, nodular or lobulated. One case in the pleura was the diaphragm, pleura, mediastinum, descending aorta and aortic window multiple nodules, combined with myasthenia gravis. However most patients have no specific clinical manifestations. Some patients may have fever, cough, fatigue, difficulty swallowing, chest discomfort, chest pain, palpitations, shortness of breath, hoarseness, loss of appetite, and fainting, [6].

Most patients had an incidental lump on physical examination. Certain clinical manifestations were associated: 9 of them had myasthenia gravis, 1 case had a special type of ectopic thymoma with pseudo-sarcoma-type stroma [7], two cases had ectopic nodular thymoma associated with Langerhans cell proliferation [4, 8], and the rest had neoplastic encephalitis, hearing loss [9], simple red cell aplastic anemia, or Good's Syndrome [10]. Tumor pathologic classification was divided into type A, type B1, type B2, type B3, type AB, and type C according to the 1999 WHO standard. Some cases were not accurately classified.

Discussion

The thymus tissue originates from the third or fourth pair of pharyngeal sacs during embryonic development, and the bilateral lobes are located in the anterior superior mediastinum at the 8th week [11, 12]. Thymoma in the thymus is a rare tumor, located in the anterior mediastinum [13-15]. It can also occur in other parts of the mediastinum, the pleura, the lung parenchyma, the pericardium, the neck, and the thyroid [5, 16-18]. The latter is called ectopic thy-

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Table 1. Clinical data of 114 cases of ectopic thymoma

Site	n	Male	Female	Age (years)	Size (cm)	Myasthenia Gravis	Pathologic classification							
							A	B1	B2	B3	AB	C	Undifferentiated	
Lung	11	3	8	8-76	3.5-15	0	0	3	1	2	1	0	4	
Pleura	6	2	4	41-74	4.0-15.0	1	1	0	0	0	1	0	4	
Chest wall	5	5	0	31-83	4.5-9.0	1	0	0	0	0	1	1	3	
Chest cavity	5	4	1	49-83	5.0-18.0	0	0	1	0	0	3	1	0	
neck	43	15	28	14-76	0.3-11.0	4	4	3	2	1	10	3	20	
Thyroid gland	17	4	13	23-77	1.2-7.3	2	3	1	0	1	3	1	8	
Pericardium	4	3	1	65-72	6.0	0	2	0	1	0	0	0	1	
Middle mediastinum	6	3	3	51-69	2.0-10.0	1	1	0	0	1	1	1	2	
Posterior mediastinum	8	4	4	40-64	3.1-8.0	0	0	3	1	0	3	0	1	
Intercostal space	1	0	1	40	6.0	0	0	0	0	0	1	0	0	
Abdomen	2	0	2	42-46	9.0-9.6	0	0	0	0	0	0	0	2	
Atria	2	1	1	69-77	5.5-6.0	0	2	0	0	0	0	0	0	
Right phrenic angle	1	0	1	48	6.0	0	0	0	1	0	0	0	0	
Anterior sternum	1	0	1	45	3.5	0	0	0	0	0	0	0	1	
Forebreast	1	1	0	47	4.5	0	0	0	0	0	0	0	1	
Left heart border	1	1	0	54	13.4	0	0	1	0	0	0	0	0	
Total	114	46	68	8-83	0.3-18.0	9	13	12	6	5	24	7	47	

moma. Ectopic thymoma accounts for only 4% of thymic tumors [2, 3]. The commonly recognized pathogenesis is abnormal migration of thymus tissue at week 6 of pregnancy [6, 19]. Ectopic thymoma is rare [20], and most of them have no typical clinical manifestations. Therefore, preoperative diagnosis is difficult and they are easily misdiagnosed as other diseases. The immunohistochemical results of case 1 suggest that lymphocytes are almost T-cell sources, with strong expression of TDT, CD99, and Ki-67, which can be found in T lymphoblastic lymphoma and thymoma, but clinically relevant examinations suggest a diagnosis of T lymphoblastoid cells. The evidence for lymphoma is insufficient, and the expression of CK19 and CD1 α support the diagnosis of thymoma, thus it is considered as ectopic thymoma. Finally, the pathologic findings of the right middle and lower lung ectopic thymoma, type B2, indicated that it invaded the chest wall. The case 2 patients was clinically asymptomatic. CT showed a soft tissue mass in the right upper lobe of the right upper lobe. The punctate calcification was considered in a pleural adenoma or teratoma. The postoperative pathology and immunohistochemistry results were diagnosed as right chest ectopic thymoma, type AB. Combined with two cases, the reason for the diagnosis could not be diagnosed before operation, mainly because ectopic thymoma is rare, and the site of occurrence is diverse, the clinical

symptoms are atypical, there is no strong clinically relevant suggestion, and the structural changes under the microscope are also major. The diagnosis of ectopic thymoma must exclude the presence of anterior mediastinal primary thymoma and should be differentiated from other related diseases.

Ectopic thymoma is mainly distinguished from the following diseases: (1) Lymphoid hyperplasia: Lymphocytic lymphoma should be differentiated from lymphoid tissue proliferation. Thymic lymphoid tissue hyperplasia refers to the preservation of normal medullary boundaries under the microscope, while there are well-developed lymphoid follicles in the thymus. Small foci-proliferating thymic epithelial cells were also seen in the proliferating thymus, but did not destroy the normal thymic structure and were not associated with the above-mentioned lymphoid follicles. Lymphocyte-associated thymoma involves the disappearance of most or all of the sub-structures of the thymus. It has a characteristic fibrous envelope containing a banded fibrous interstitium with sharp angles and serum surrounding the blood vessels "lake". (2) Lung cancer: Ectopic thymoma in the lung should be differentiated from lung cancer. Lung cancer often has lobulation and burrs. Non-invasive pulmonary ectopic thymoma tumor and lung tissue interfaces are relatively smooth. Among them, small cell lung cancer

cer tumor cells can occasionally form a chrysanthemum group, and the chrysanthemum-like structure is keratin positive, but most small cells do not stain, and small cell carcinoma will have membrane-enveloped secretory granules under an electron microscope. (3) Lymphoblastic lymphoma: Ectopic thymoma has a lobular structure in which thymic bodies are visible. Immunohistochemical results showed that the epithelial cells in the lobules were reticular and could be differentiated from lymphoma [21]. Under the electron microscope, well-developed intercellular desmosomal junctions were observed between adjacent protrusions of ectopic thymoma epithelial cells, and lymphoma shows no such expression. (4) Teratoma: Both ectopic thymoma and teratoma can undergo cystic changes, and the structure under the microscope changes greatly. The two should be identified when diagnosed. Teratoma is imaged as a cyst or cystic mass, and the internal space of the tumor can be used as a marker for benign teratoma. Teratoma can usually be observed in mixed squamous epithelium, glia, fat, bone and cartilage, but ectopic thymoma usually does not have these manifestations. (5) Malignant fibrous histiocytoma: The atypia of the cells is obvious, and there may be mitotic figures. There are not many scattered lymphocytes in the interstitium, there is no mutual migration relationship with the epithelial cells, and it does not express CK. (6) Papillary thyroid carcinoma: Ectopic thymoma occurring in the thyroid gland should be differentiated from papillary thyroid carcinoma. Papillary carcinoma can occur in any part of the thyroid gland. A few lesions can be cystic, usually 2-3 cm on average. The lesion is hard, and usually white with calcification. The microscopic thyroid papillary carcinoma cell nucleus is a transparent ground glass, and most of the papillae have a fibrovascular cores.

Conclusion

In a few cases of ectopic thymoma, the presence of myasthenia gravis [22] may be diagnostically helpful. However, most patients do not have myasthenia gravis, so the clinician should pay attention to this. To fully understand and master the corresponding knowledge of thymoma and ectopic thymoma, ectopic thymoma should be considered in the diagnosis of related diseases, and the rate of misdiagnosis should be minimized. Ectopic thymoma, like thymoma, has malignant potential. Surgical

treatment is the main choice in clinical practice, and further radiotherapy is not required depending on pathologic classification.

Disclosure of conflict of interest

None.

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