

# An Unusual Ectopic Thymoma in the Lung and Anterior Mediastinum: A Case Report

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## Case Report

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# Abstract

**Background:** Ectopic thymoma, a subtype of thymomas, is a rare clinical entity. Understanding the pathogenesis and evolution of Ectopic thymoma may lead to greater insight into tumor initiation and maintenance and may guide therapeutic interventions. We report a case of a multiple thymoma in the lung and anterior mediastinum.

**Case presentation:** we presented a case of 62-year-old man with type A ectopic pulmonary thymoma and thymoma in the anterior mediastinum, which were diagnosed postoperatively. Mediastinal lesion resection and thoracoscopic pulmonary wedge resection were performed. The tumors were completely resected, and the patient was disease-free and without recurrence. we performed whole-exome sequencing (WES), and found eight gene mutations that was co-mutated in both lesions. Consistent with a previous exome sequencing analysis of Thymoma and Thymic Carcinoma, HRAS was also observed in mediastinal lesion and lung lesion tissues. We also evaluated the intratumor heterogeneity of nonsilent mutations, and the mediastinal lesion tissue has higher degree of heterogeneity in detected variants, and the pulmonary tissue has a relatively low amount of variant heterogeneity.

**Conclusions:** Ectopic thymoma is a highly rare clinical entity. Full recognition of its Molecular characteristics will help to better diagnose this disease.

## Background

Thymomas are neoplasms of the thymic gland that arise in the anterosuperior mediastinum. Thymic neoplasms, such as thymoma and thymic carcinoma, arise mainly in the anterosuperior mediastinum, while ectopic thymomas account for only 4% of all thymomas[1]. The most common locations of ectopic thymoma are the cervical region followed by the lungs and pleura. Other locations also have been reported, such as thyroid gland, middle/posterior mediastinum and pericardium[2]. Here, a rare case of thymoma in the anterior mediastinum, and simultaneous intrapulmonary thymoma was reported. The clonal architecture of tumors plays a vital role in their pathogenesis and invasiveness. Intratumour diversity hampers treatment success in many types of solid tumours, and understanding its effect on the course of Thymomas and treatment efficacy is an unmet scientific and clinical need. Therefore, additional information regarding the genetic changes associated with Thymomas has the potential to facilitate improvements in the prevention and treatment of this disease. In our study, together with whole-exome sequencing (WES), revealed a set of cancer-related genes that are recurrently mutated in Thymomas, including HRAS. We also evaluate the intratumor heterogeneity of nonsilent mutations by PyClone, the result shows a case of a multiple thymoma in the lung and anterior mediastinum .

## Case Presentation

A 62-year-old man visited hospital, because of some symptoms of dizziness without obvious symptom, with nausea, but no abdominal pain, muscle weakness, distension and palpitation from him six days ago.

On image diagnosis, Positron emission tomography/CT (PET/CT) showed soft-tissue density lesions of the left lower lobes of the thyroid with calcification (Figure 1A-1D), multiple nodules of different sizes in bilateral lungs (Figure 1E-1F). A magnetic resonance imaging (MRI) showed some findings from the mediastinum and lungs, including (1) a mass (45 mm × 30 mm × 38 mm) in the superior mediastinum of the left lobe of thyroid and fat space between the lesion and the surrounding mediastinum vascular, trachea, esophagus and upper thyroid gland; trachea shifted to the right, and the tumor showed equal T1 and long T2 mixed signals with obvious heterogeneous enhancement (Figure 1G-1H); (2) multiple nodules with smooth margin in bilateral lungs, especially, the largest one (19 mm × 18 mm) was located in the left lower lobe of lung, and displayed marked enhancement (Figure 1I). Further Pathological results revealed the possibility of type A thymoma (Figure 2), considering thymoma involving lung or ectopic pulmonary in the lung.

According to her medical inspection, the patient was recommended for a surgery treatment including mediastinal lesion resection and thoracoscopic pulmonary wedge resection and went through. Four tumor tissues were easily dissected from adjacent structures and completely removed. Subsequently, these tumor tissues were further analyzed. The histopathological findings from one tumor tissue showed a thymoma type A in the anterior mediastinum (Figure 3A), and Immunohistochemical results also showed that the expression of PCK and P40 in tumor cells revealed positive and the expression of CD5, CD20, CD117, TdT, Ki67 revealed negative (Table 1). In addition, multiple thymomas in the lungs (type A) which were considered as intrapulmonary thymomas (Figure 3B).

Table 1

Results of immunohistochemical staining on the tumor tissues originating from lung and anterior mediastinum.

<b>Lung</b>	
p40, PCK	Positive
TTF-1, Syn, CD34, STAT6, SMA, S100, Desmin, ALK	Negative
<b>Anterior mediastinum</b>	
p40, PCK	Positive
CD5, CD20, CD117, TdT	Negative
Ki67	5%
<b>Abbreviations:</b> PCK, phosphoenolpyruvate carboxykinase; TTF-1, thyroid transcription factor 1; Syn, synapsin; STAT-6, signal transducer and activator of transcription 6; SMA, smooth muscle actin; ALK, anaplastic lymphoma kinase; TdT, terminal deoxynucleotidyl transferase. FDG-PET, fluorodeoxyglucose -positron emission tomography; CT-SCAN, computerized tomography (CT) scan.	

The patient was healed from surgery and no recurrence was found by examination. To obtain insights into genetic alterations that characterize the tumor heterogeneity of thymomas, we examined a patient with type A ectopic pulmonary thymoma and thymoma, and performed whole-exome sequencing

analysis the resected tumor tissues. We identified 383 and 269 somatic non-synonymous single-nucleotide variations (SNVs) in coding regions in mediastinal lesion and lung lesion tissues, respectively (Supplementary Table 1 and Table 2). And direct comparison between the mediastinal lesion and pulmonary sample reveal overlapping frequencies of commonly mutated genes, only 8 mutations were shared (Supplementary Table 3). Consistent with a previous exome sequencing analysis of Thymoma and Thymic Carcinoma [3], mutations in cancer gene census genes, HRAS was observed in mediastinal lesion and lung lesion tissues. We compared results from 10 canonical signaling pathways and cancer driver genes with frequent genetic alterations in our study, using recently published mutational profiles of multiple samples from TCGA publications [4, 5], 18 genes (18/335) and 16 genes (16/299) were identified in ectopic pulmonary thymoma, respectively. And 24 genes (24/335) and 26 genes (26/299) were tested in mediastinal thymoma, respectively. Additionally, compared to the DNA Repair and DNA Damage Signaling Pathways [6], there are 8 genes (8/229) and 17 genes (17/229) that contain mutation found in ectopic pulmonary thymoma and mediastinal thymoma, respectively. To further understand the function of the identified gene mutations, we reviewed literature reports addressing these mutations and found that at present, most of these mutations have not been reported to be related to human tumors.

To gain further insight into the accumulation of genetic alterations, we constructed phylogenetic trees of disease evolution taking all mutations in mediastinal thymoma and ectopic pulmonary thymoma. We used the detected SNV profile for each sample to analyze the corresponding clonal/subclonal architecture using PyClone. Clustering of mutations revealed the subclonal structure of mediastinal thymoma and ectopic pulmonary thymoma in patient harboring multiple mutations. The mediastinal thymoma showed a wide spectrum of modes over clonal/subclonal frequencies ranging from one to five clusters. Mutation of PIK3CA was clustered together in subclone-1. Mutation of MUC17 was clustered in subclone-3. BRCA2, ALK and PIK3R1 mutations were clustered together in subclone-6. Driver gene mutation was not found in subclone-2 and subclone-4. PyClone detected two clusters in ectopic pulmonary thymoma. Mutation of MTOR was clustered in subclone-5, and ZNF440 mutations were clustered together in subclone-7. When interpreting the data, the mediastinal lesion tissue appeared to have a higher degree of heterogeneity in detected variants, and the pulmonary tissue showed a relatively low amount of variant heterogeneity.

## Discussion And Conclusions

Ectopic thymomas are a rare cancer. As a subtype of ectopic thymoma, ectopic pulmonary thymoma accounts for 20% [2], which was first described by McBurney et al. in 1951. Up to 2017, only 37 cases of ectopic pulmonary thymoma have been reported [7]. The histogenesis of ectopic thymomas remains unclear. Displacement, one of the theories explaining the existence of such tumors, is widely accepted. Embryologically, the thymus develops from the third and fourth pharyngeal pouches and migrates into the anterosuperior mediastinum by the fifth or sixth week of gestation [1]. Ectopic thymomas may develop from the displacement of thymic tissue during embryogenesis. This theory explains proficiently the existence of thymic tissue in the cervical region, thyroid and pericardium. However, it fails to explain the

presence of thymic tissue in the lung, because the pulmonary system develops much earlier than the thymus[8]. Therefore, another popular hypothesis, stem cell theory, was proposed that ectopic thymomas could originate from stem cells. Primary intrapulmonary tumors deriving from ectopic tissues not native to the lung, such as meningiomas[9] or melanoma[10], support the hypothesis that ectopic thymic neoplasms may be able to originate from stem cells. In our case, the patient was diagnosed as an ectopic pulmonary thymoma, as well as a thymoma in thymus. By applying the stem cell theory, it made sense that the patient in our report developed thymomas in both locations.

Though the cytologic features of ectopic thymomas and thymic carcinoma are identical to those of mediastinal thymomas and thymic carcinoma, the correct diagnosis is extremely challenging to make because of the rarity of being found in such an unusual location and the variety of histology patterns seen. Some pathologists lack of awareness of this entity and lack of typical features of the thymoma or thymic carcinoma make the diagnosis even more difficult. The exact diagnosis is based on histologic findings, and ectopic pulmonary thymoma displays the same characteristic histological features of mediastinal thymoma[11]. However, it is easy to confuse this lesion with other tumors. To reach this purpose, several IHC markers are recommended, such as p40, TdT, SMA, S100, CD5 and desmin[7, 12, 13]. The strong collagen IV deposits among the spindle cells and the extensive co-expression of cytokeratins and CD20 were considered highly diagnostic for type A thymoma according to the World Class Organization classification system of TET. The hemangiopericytic pattern is a frequent feature in spindle cell (type A) thymoma. Furthermore, the diagnostic value of the co-expression of cytokeratins and CD20 was considered. In our case, positive staining for p40 and PCK were observed in both tumor tissues, while the other IHC markers were negative. These results together with the histological features revealed by hematoxylin and eosin stain helped the diagnosis of type A thymomas in the anterior mediastinum and lung according to the WHO classification. Type A thymoma are usually characterized by a low grade of malignancy.

The recommended treatment of thymomas is surgical resection because of the significant better survival rate[14]. Besides, adjuvant therapy like radiation or chemotherapy was suggested in case of the incomplete resection or expansion of the tumor tissue. In our case, the masses were low-risk thymomas without invasion, therefore, no adjuvant therapy after surgical treatment was conducted.

Established the thymic tissue origin of the lesion the metastatic nature was the most probable nevertheless it was excluded and the tumour considered primary because both FDG-PET and total body CT-SCAN didn't detect other lesions or ectopic thymus. In our study, we further performed WES to reveal some molecular profiles. Literarily, Petrini *et al.* analyzed 28 thymic epithelial tumors (TETs) and identified a high frequency of GTF2I (general transcription factor II I) mutation at type A thymomas but not in the aggressive subtypes[15]. In our case, we did not find GTF2I mutation in either ectopic pulmonary thymoma or mediastinal thymoma. Eight genes were found to be co-mutated in both lesions, among which, *HRAS*, a driven gene, was included. *HRAS* mutation was identified as one of the recurrent somatic mutations in thymic carcinoma (the most aggressive type of TETs)[16]. In addition, combined with

previous published mutational profiles [4-6], the mutational landscape of both mediastinal lesion and lung lesion tissues have a significant different.

Patial heterogeneity complicates the analysis of solid tumors, as distinct regions of a tumor may harbor different subclonal populations. Assaying multiple regions of heterogeneous tumors should assist in uncovering the full spectrum of mutations and subclones present in a tumor and help identify the spatial origins of subclones. Through sequencing multiple surgically resected tumor regions, we were able to unravel both the extent of genomic heterogeneity and the evolution history of mediastinal thymoma and ectopic pulmonary thymoma. we constructed phylogenetic trees of disease evolution taking all mutations in mediastinal thymoma and ectopic pulmonary thymoma. PyClone detected two clusters in ectopic pulmonary thymoma and the mediastinal thymoma showed a wide spectrum of modes over clonal/subclonal frequencies ranging from one to five clusters. For the patient, the mediastinal lesion and pulmonary tissue were each polyclonal, and the clonal populations differed from one thymoma to another, the mediastinal lesion tissue had a highly degree of heterogeneity and the pulmonary tissue showed a relatively low amount of variant heterogeneity. The result implied the case represents a disease of multicentric origin.

In conclusion, we reported a rare case with type A ectopic pulmonary thymoma and mediastinal thymoma. Our data demonstrated an evident heterogeneity between ectopic pulmonary thymoma and mediastinal thymoma.

## **Declarations**

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## **Authors' contributions**

YZ collected the clinical data and drafted the manuscript. LW, ZL and QL made the pathological diagnosis. YZ and KZ offered assistance in image selection. LW, ZL and RM made revision to the final manuscript and provided the funding support. All authors read and approved the final manuscript.

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## **Availability of data and materials**

The datasets generated and analyzed during the current study are available from the corresponding authors on reasonable request.

## Ethics approval and consent to participate

This case study was approved by the Ethics Committees of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

## Consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

## Competing interests

The authors declare that they have no competing interests.

## Author details

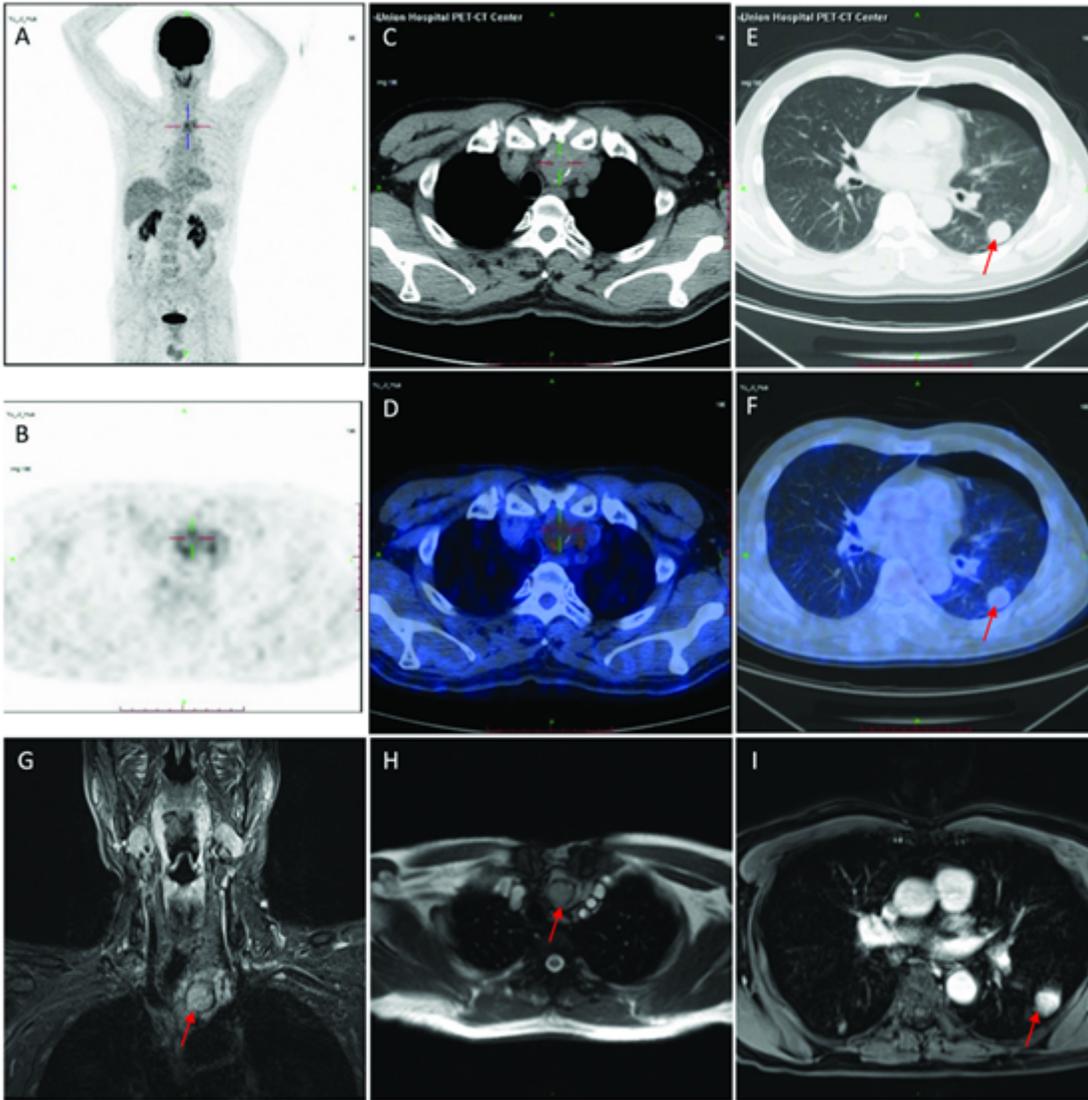
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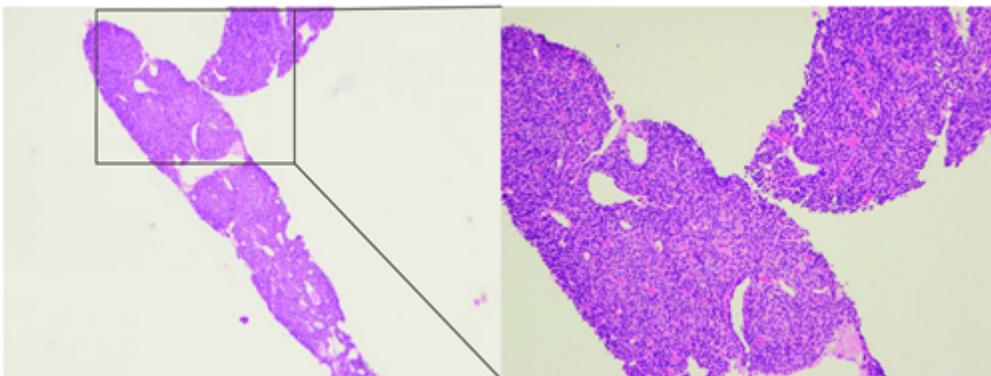
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## Figures



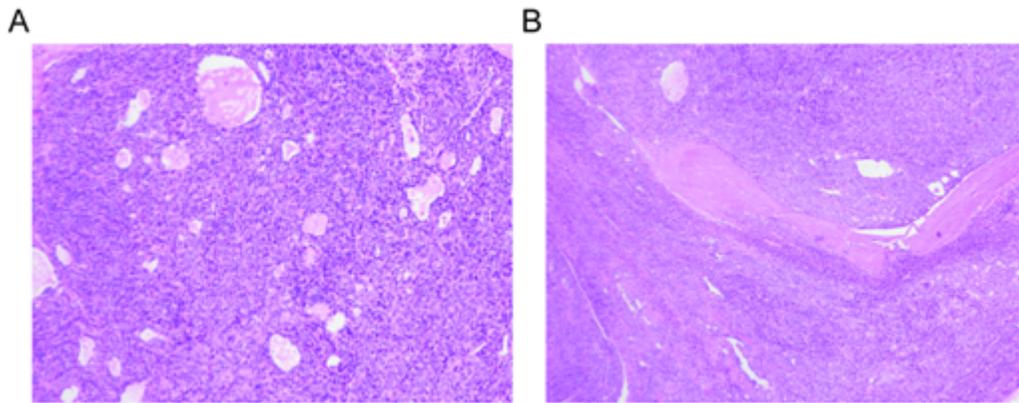
**Figure 1**

Imaging findings of the patient. (A-D) PET/CT showed a mass in the mediastinal portion. (E-F) PET/CT showed nodules (arrow) in lung. (G-H) MRI examination showed a 4.5 cm × 3.0 cm × 3.8 cm mass (arrow) in the mediastinal portion. (I) MRI examination showed multiple nodules in the lung. The arrow indicated a 1.9 cm × 1.8 cm nodule in the left lower lobe of lung.



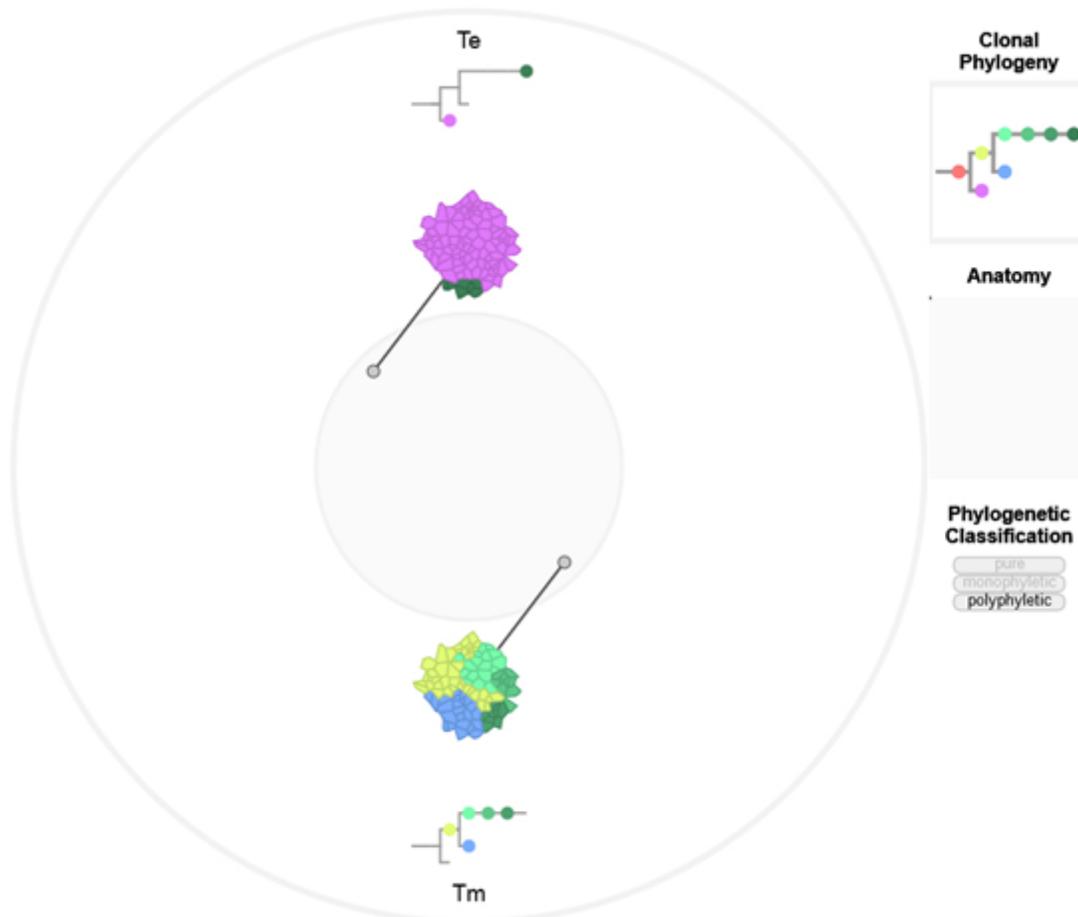
**Figure 2**

Histopathological result showed a type A thymoma pattern (hematoxylin and eosin staining;  $\times 100$ ).



**Figure 3**

Postoperative histopathological results. (A) Microscopic view of thymoma type A in the anterior mediastinum. (B) Microscopic view of ectopic pulmonary thymomas type A in the left lower lung. Magnification:  $\times 40$ .



## Figure 4

Clone phylogenies and sample clone mixtures. A clone phylogeny is shown for the patient, with distinct clonal genotypes color-coded. The clonal composition of each sample is depicted as a schematic tumor, with the coloring of 'cells' proportional to the prevalence of each clone. Samples are arrayed in a circle, with constituent clones from the overall clone phylogeny represented in an outer circle. Tm: mediastinal thymoma. Te: ectopic pulmonary thymoma.

## Supplementary Files

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- [SupplementaryTable1andTable2andTable3.xlsx](#)