Primary thymic papillary adenocarcinoma with a rare CD5/CD117-negative and PAX8/WT1-positive immunophenotype: A case report

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Received December 5, 2025; Accepted May 6, 2026

DOI: 10.3892/ol.2026.15757

Abstract. Primary thymic papillary adenocarcinoma (PAT) is an exceptionally rare epithelial malignancy that poses substantial diagnostic challenges due to its non-specific radiological presentation and highly heterogeneous immunophenotype. The present study reports a case of early-stage PAT in a 48-year-old man with a long-standing history of rheumatoid arthritis. Chest computed tomography (CT) revealed a 3.3-cm, well-circumscribed, lobulated anterior mediastinal nodule demonstrating homogeneous contrast enhancement, radiologically mimicking a benign thymic cyst or thymoma. Following complete resection via video-assisted thoracoscopic surgery (VATS), histopathological examination demonstrated a cystic and solid tumor with conspicuous papillary architecture. Diagnostic interpretation was confounded by an atypical immunoprofile: The tumor was negative for the traditional thymic carcinoma markers CD5 and CD117, yet exhibited diffuse expression of paired box gene 8 and WT1, thereby closely resembling metastatic renal cell carcinoma or mesothelioma. A diagnosis was strongly supported through a rigorous process of exclusion, integrating an extended negative immunohistochemical panel (including Spalt-like transcription factor 4, thyroid transcription factor-1 and D2-40) with the morphological identification of residual atrophic thymic tissue at the tumor periphery. The tumor was classified as Masaoka-Koga stage I PAT, and the patient remained free of recurrence at the 6-month postoperative follow-up. The present case highlights the diagnostic pitfalls of PAT, particularly its deceptively benign imaging appearance and unusual immunophenotype. It emphasizes that CD5/CD117 negativity does not preclude a thymic origin, underscoring the necessity of a comprehensive, exclusion-based approach for accurate diagnosis.

Introduction

Primary thymic adenocarcinoma (PTA) represents a rare subgroup of mediastinal neoplasms. In the International Thymic Malignancy Interest Group database, thymic adenocarcinoma accounted for 29 of 6,097 thymic epithelial neoplasms (0.48%) and 11 of 706 thymic epithelial malignancies/carcinomas (1.6%) (1,2). Within this category, the papillary adenocarcinoma (PAT) subtype is particularly uncommon, with existing literature restricted primarily to sporadic case reports (3-7). Establishing an accurate diagnosis of PAT poses significant challenges due to the frequent absence of specific radiological features-often mimicking benign cysts - and its histological overlap with metastatic adenocarcinomas originating from the lung, thyroid or kidneys. Furthermore, although CD5 and CD117 are traditionally regarded as canonical diagnostic markers for thymic carcinoma, their expression in adenocarcinoma subtypes is inconsistent, potentially leading to the erroneous exclusion of a primary thymic origin. Therefore, clinicopathological correlation and an exclusion-based immunohistochemical strategy are essential when evaluating papillary adenocarcinoma in the anterior mediastinum.

The current study presents a case of early-stage PAT in a 48-year-old man with a history of rheumatoid arthritis (RA). This case is clinically instructive because it presented with deceptively benign imaging, a CD5/CD117-negative phenotype, and aberrant diffuse expression of paired box gene 8 (PAX8) and WT1, all of which complicated the diagnostic assessment. The present report aims to elucidate the diagnostic pitfalls associated with this unusual immunoprofile and to emphasize the necessity of a rigorous, exclusion-based diagnostic

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Abbreviations: AFP, α-fetoprotein; CEA, carcinoembryonic antigen; CT, computed tomography; HCG, human chorionic gonadotropin; HU, Hounsfield units; PAT, papillary adenocarcinoma of the thymus; PTA, primary thymic adenocarcinoma; VATS, video-assisted thoracoscopic surgery

Key words: PTA, papillary adenocarcinoma, immunophenotype, diagnostic challenge, VATS

strategy integrating radiological findings, histomorphology, broad immunohistochemical evaluation and clinicopathological correlation to distinguish primary PAT from metastatic mimics, such as renal cell carcinoma or mesothelioma.

Case report

A 48-year-old man was admitted to Shiyan Taihe Hospital (Hubei University of Medicine) following the incidental detection of an anterior mediastinal mass during a routine health examination 1 week prior. A subsequent chest computed tomography (CT) scan, performed at Zhuxi County People's Hospital (Hubei, China) during an RA evaluation, confirmed the presence of an anterior mediastinal space-occupying lesion. The patient denied respiratory symptoms, including cough, chest tightness, dyspnea and hemoptysis, and exhibited no clinical manifestations suggestive of myasthenia gravis, such as ptosis or limb weakness. The patient had a >10-year history of RA managed intermittently with unspecified oral medications at local clinics; the exact pharmacological regimen was unknown.

Subsequent contrast-enhanced chest CT demonstrated a 3.3x2.0 cm, irregularly lobulated anterior mediastinal mass with well-defined margins and preserved surrounding fat planes. The lesion exhibited moderate homogeneous enhancement, with attenuation values increasing from 15 Hounsfield units (HU) on unenhanced images to 39 HU following contrast administration (Fig. 1A-C). Additional findings included scattered, tiny bilateral pulmonary nodules and several fibrotic foci in the right middle lobe.

To exclude metastatic disease, a comprehensive systemic workup was performed. Non-contrast cranial CT revealed a sphenoid sinus cyst, while ultrasonography of the thyroid and cervical lymph nodes was unremarkable. Abdominal and urinary tract ultrasonography revealed mild hepatic steatosis and small renal calculi, but no space-occupying lesions. Transthoracic echocardiography revealed mild left atrial enlargement and interventricular septal thickening, without gross structural abnormalities.

Laboratory investigations revealed mild elevations in the white blood cell count ($9.74x10^9$/l; reference range, 3.5-$9.5x10^9$/l), absolute lymphocyte count ($3.21x10^9$/l; reference range, 1.1-$3.2x10^9$/l), and absolute monocyte count ($0.70x10^9$/l; reference range, 0.1-$0.6x10^9$/l). Glycated hemoglobin was elevated at 6.62% (reference range, 3.6-6.0%). Serum biochemistry showed mildly decreased total protein (60.46 g/l; reference range, 65-85 g/l), albumin (36.18 g/l; reference range, 40-55 g/l), and calcium (2.07 mmol/l; reference range, 2.11-2.52 mmol/l), alongside elevated transferrin (4.63 g/l; reference range, 2-4 g/l). Serum tumor markers [including α-fetoprotein (AFP), carcinoembryonic antigen (CEA) and human chorionic gonadotropin (HCG)], coagulation parameters, erythrocyte sedimentation rate, and the antinuclear antibody profile were all within normal limits.

Given the localized nature of the mass and the absence of distant metastasis, the patient underwent video-assisted thoracoscopic surgery (VATS) resection under general anesthesia. Intraoperative exploration revealed a solitary, firm, solid nodule with a pseudocapsular appearance and clear demarcation from the surrounding tissues, without obvious invasion into adjacent structures. The mass was completely excised *en bloc* with the surrounding thymic adipose tissue. The operative course was uneventful, and intraoperative frozen-section analysis was indicative of a malignant neoplasm. Early post-operative CT images obtained several days after surgery confirmed removal of the anterior mediastinal lesion and demonstrated the surgical bed after resection (Fig. 1D-F).

Gross examination of the formalin-fixed specimen revealed an irregular, gray-yellow tissue fragment measuring 5.5x4.2x2.5 cm with a visible pseudocapsule. Serial sectioning exposed a 4.2x2.2x1.8 cm cystic and solid nodule. The solid areas were gray-white to gray-red with an intermediate consistency, while the cystic spaces possessed smooth inner walls (data not shown).

Microscopically, the tumor was relatively well-circumscribed; however, a true fibrous capsule was completely absent. The neoplastic cells formed prominent papillary structures and were characterized by low cuboidal to low columnar morphology, scant cytoplasm and rare mitotic figures. Notably, residual atrophic thymic tissue was identified at the tumor periphery (Fig. 2).

Immunohistochemically, the tumor cells exhibited diffuse positivity for PAX8, WT1, cytokeratin (CK)8, epithelial membrane antigen (EMA), CK19, pan-cytokeratin (CK-pan) and CD56, alongside focal positivity for calretinin. The Ki-67 proliferation index was ~10%. An extensive panel of negative markers systematically excluded other entities: Traditional thymic markers (CD5, CD117), pulmonary and thyroid markers [thyroid transcription factor-1 (TTF-1) and thyroglobulin (Tg)], germ cell markers [Spalt-like transcription factor 4 (SALL4), AFP, inhibin-α and steroidogenic factor 1], mesothelial markers (D2-40), squamous/basal markers (p63, p40 and CK5/6), vascular/mesenchymal markers (CD31, CD34, CD99 and vimentin) and additional epithelial markers (CK7, Ber-EP4 and CEA) were all completely negative (Figs. 3 and 4). Molecular analysis revealed an intact *CDKN2A* gene and a wild-type *BRAF* (V600E negative) status.

This comprehensive clinicopathological and molecular evaluation effectively excluded mesothelioma and metastatic carcinomas from the lung, thyroid and genitourinary tract. Consequently, the identification of residual atrophic thymic tissue, together with the clinicopathological and immunohistochemical findings, strongly supported a diagnosis of primary thymic PAT. Given the early stage of the disease (Masaoka-Koga stage I) (8) and the achievement of complete surgical resection, the patient was discharged on postoperative day 7 without adjuvant chemoradiotherapy. At the 6-month follow-up, a repeat chest CT demonstrated no evidence of local recurrence (Fig. 5). The previously noted tiny pulmonary nodules remained stable in size and morphology, supporting their benign etiology and confirming the absence of distant metastasis.

Discussion

The clinicopathological characteristics of previously reported thymic PAT cases are summarized in Table I. These cases demonstrate considerable heterogeneity in patient age, tumor size, associated thymic lesions, immunophenotype, molecular alterations and clinical outcome. In this context, the present

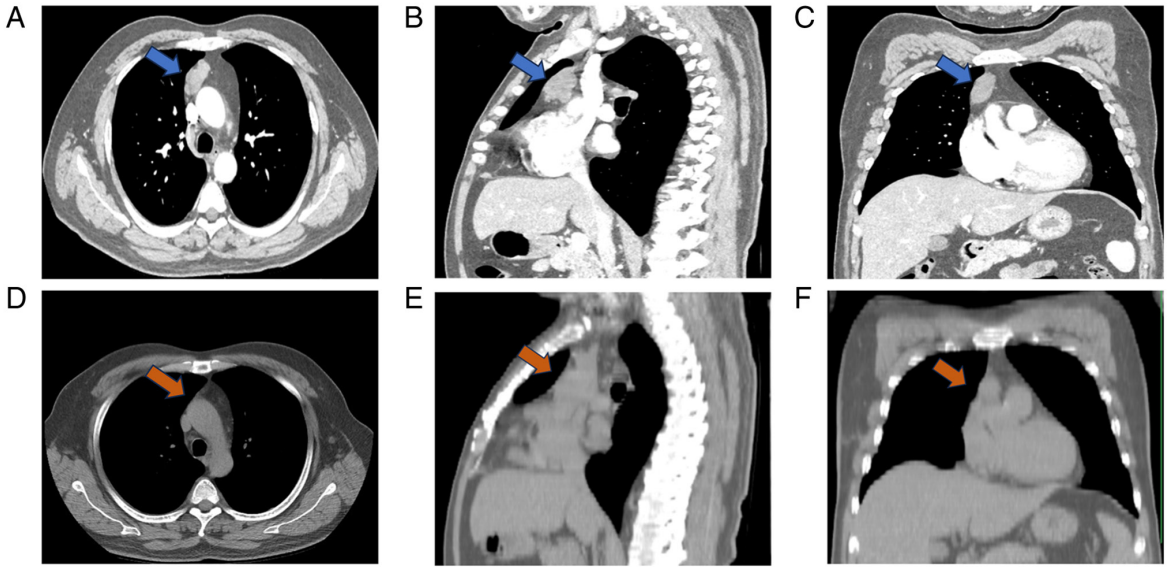

Figure 1. Pre-operative and post-operative radiological assessment of the anterior mediastinal tumor. (A-C) Pre-operative contrast-enhanced chest CT scans (mediastinal window). (A) Axial view; (B) sagittal view; and (C) coronal view. The blue arrows indicate a well-circumscribed, lobulated soft-tissue mass located in the anterior mediastinum. Note the clear interface between the tumor and the surrounding mediastinal fat and great vessels, suggestive of a non-invasive lesion. (D-F) Post-operative chest CT images after tumor resection. (D) Axial view; (E) sagittal view; and (F) coronal view. The images confirm the complete resection of the lesion with no evidence of local recurrence.

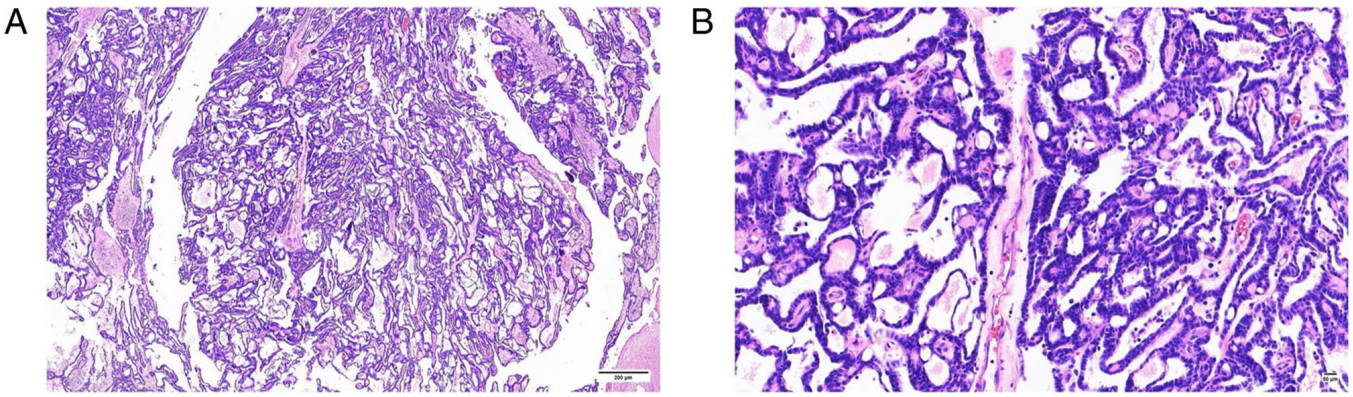

Figure 2. Histopathological features of the primary thymic papillary adenocarcinoma (hematoxylin and eosin staining). (A) Low-power magnification (magnification, x40) reveals the tumor exhibiting a prominent papillary growth pattern. A pseudocapsule (compressed adjacent tissue) is visible, separating the tumor nest from the adjacent mediastinal adipose tissue. (B) Medium-power magnification (magnification, x200) demonstrates the characteristic papillary architecture. The papillae are supported by delicate fibrovascular cores and lined by a single layer of cuboidal to low-columnar epithelial cells with mild nuclear atypia. No significant necrosis or high mitotic activity is observed.

early-stage PAT is particularly noteworthy because of its deceptively benign imaging features, concurrent CD5/CD117 negativity and aberrant PAX8/WT1 positivity. This unusual immunophenotypic profile may closely mimic metastatic renal cell carcinoma or mesothelioma and may also lead to the erroneous exclusion of a primary thymic origin if conventional thymic carcinoma markers are overemphasized. The first major diagnostic challenge was the subtle and misleading radiological presentation. Typical thymic carcinoma often presents as a large, invasive mass with irregular margins, frequently accompanied by necrosis or calcification (9). By contrast, the chest CT in the present patient demonstrated a well-circumscribed, lobulated anterior mediastinal nodule with preserved surrounding fat planes and homogeneous contrast enhancement. These ‘indolent-appearing’ characteristics can easily lead to misinterpretation as a benign thymoma or an atypical thymic cyst. Notably, macroscopic pathological examination confirmed a cystic and solid cut surface, suggesting that microcystic architecture may have radiologically masked the lesion's malignant nature. Zaitlin *et al* (7) emphasized that thick-walled cysts or cystic and solid nodules in the anterior mediastinum should raise suspicion for malignancy, even when radiologically benign in appearance. The present case reinforces the notion that benign imaging features alone cannot exclude rare malignancies. For any indeterminate anterior mediastinal nodule, surgical exploration serves not only as a therapeutic intervention but also as the definitive diagnostic modality and a critical strategy for preventing missed malignancies (3,10).

The most clinically instructive and diagnostically challenging aspect of the present case was its markedly

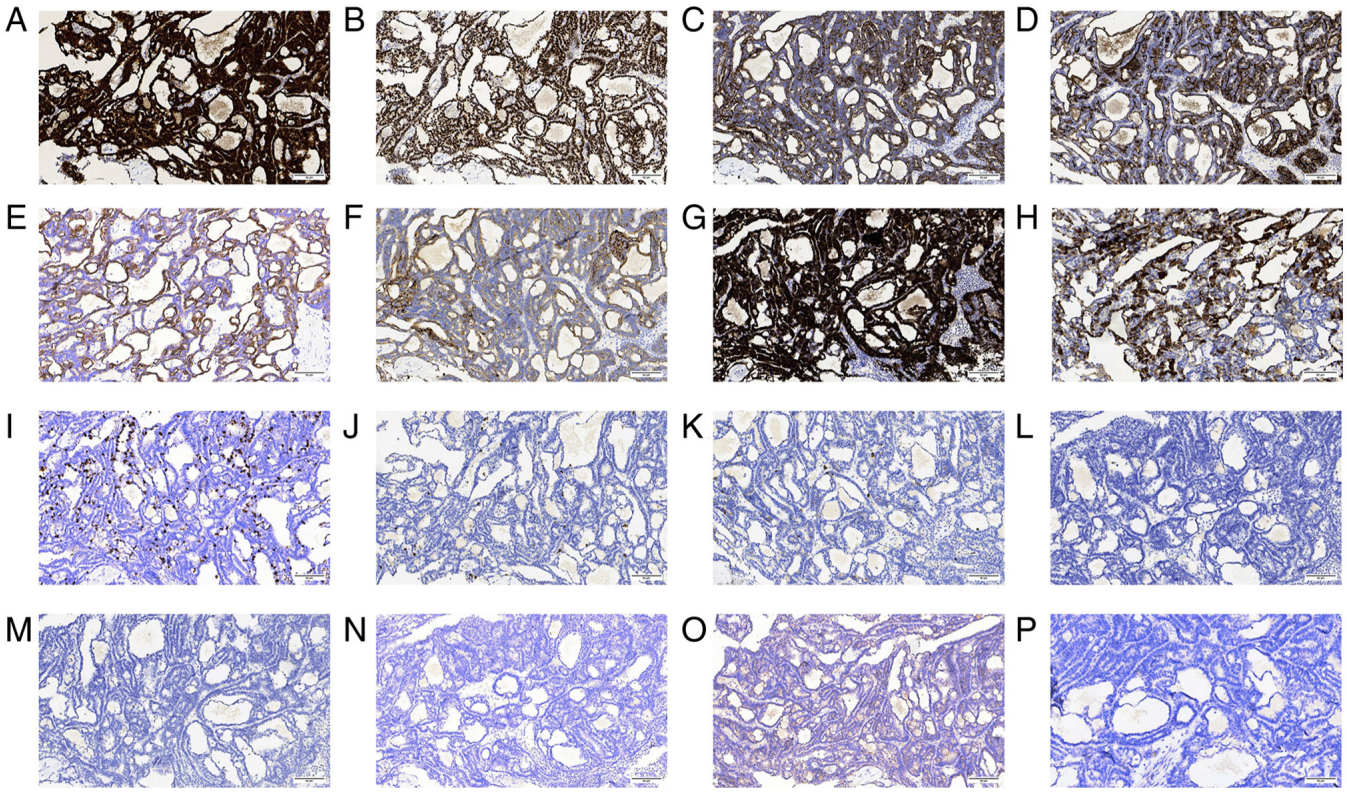

Figure 3. Positive and selected negative immunohistochemical staining images. Tumor cells showed diffuse nuclear or cytoplasmic positivity for (A) PAX8, (B) WT1, (C) CK8, (D) EMA, (E) CK19, (F) CK-pan, and (G) CD56. Focal positivity was observed for (H) calretinin. (I) Ki-67 staining demonstrated a proliferation index of ~10%. By contrast, negative staining was observed for (J) CD5, (K) CD117, (L) TTF-1, (M) Tg, (N) SALL4, (O) AFP and (P) inhibin-α. Magnification, x200. EMA, epithelial membrane antigen; CK, cytokeratin; CK-pan, pan-cytokeratin; Tg, thyroglobulin; SALL4, Spalt-like transcription factor 4; PAX8, paired box gene 8; TTF-1, thyroid transcription factor-1.

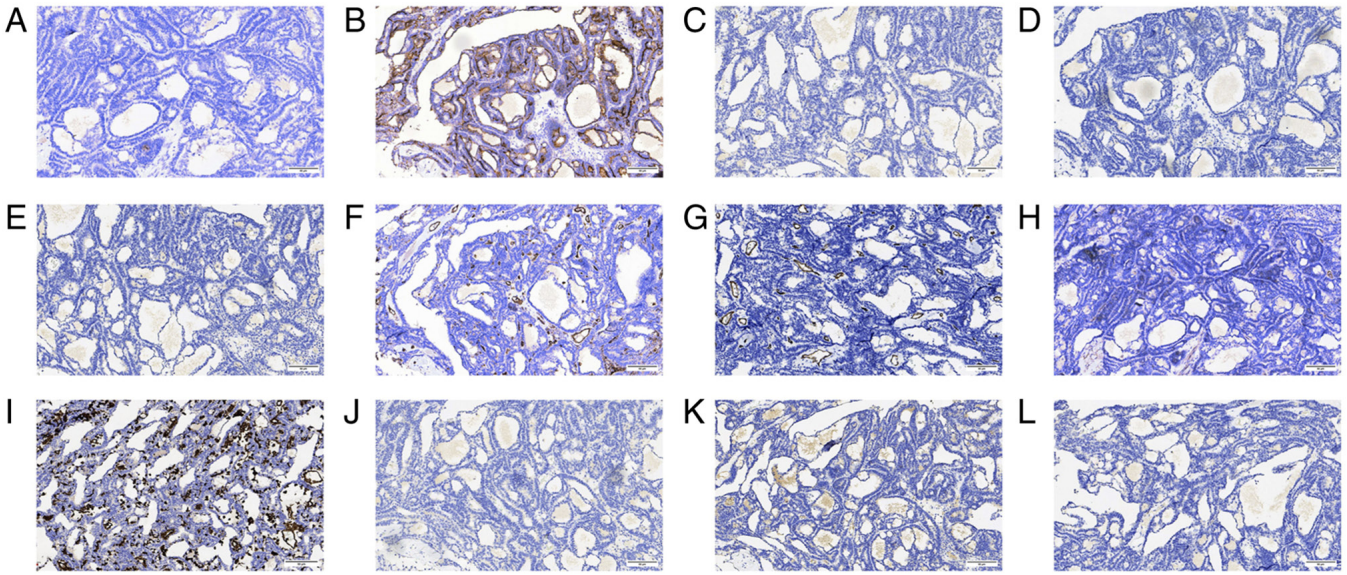

Figure 4. Extended negative immunohistochemical staining profile. Tumor cells exhibited negative staining for (A) SF-1, (B) D2-40, (C) p63, (D) CK5/6, (E) p40, (F) CD31, (G) CD34, (H) CD99, (I) vimentin, (J) CK7, (K) Ber-EP4 and (L) CEA. Magnification, x200. SF-1, steroidogenic factor 1; CK, cytokeratin.

heterogeneous immunophenotype, which was highly susceptible to misinterpretation. First, CD5 and CD117 (c-kit) have long been regarded as 'canonical' markers for the diagnosis of thymic carcinoma. This highlights that while these markers are consistently expressed in thymic squamous cell carcinoma, their loss in adenocarcinoma subtypes may be more frequent than previously recognized (11,12). Second, analysis of the CK profile revealed a striking pattern: while the tumor cells exhibited diffuse expression of the epithelial markers EMA, CK-pan, CK8 and CK19, they were completely negative for p63, p40 and

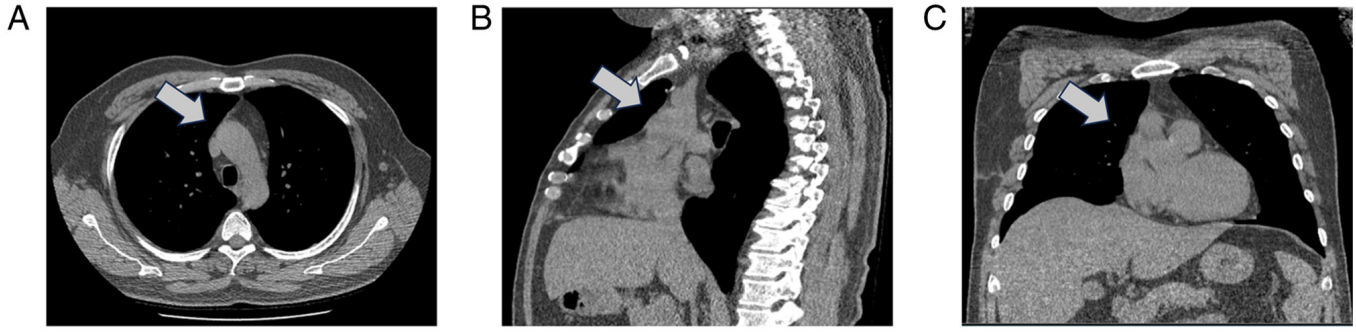

Figure 5. Postoperative follow-up chest CT images at 6 months. (A-C) Postoperative 6-months follow-up chest CT images showing no evidence of recurrence in the surgical area (gray arrows). (A) Axial view; (B) sagittal view; and (C) coronal view.

CK5/6. This finding is critical, as the absence of p63 and p40 strongly argues against thymic squamous cell carcinoma and most types of thymoma, supporting instead an adenocarcinomatous differentiation (2,13). Notably, CK7 was also negative, contrasting with the typical CK7 positivity observed in the majority of PTAs (14). This further underscores the unique CK expression profile of the current tumor. Additionally, we observed aberrant CD56 expression. Although CD56 is commonly used as a neuroendocrine marker, the overall immunohistochemical panel (including negative synaptophysin and other neuroendocrine markers), together with the absence of typical neuroendocrine morphologic features (such as rosette formation or trabecular architecture), indicates that the CD56 positivity represents non-specific aberrant expression rather than true neuroendocrine differentiation.

Given this complex immunophenotype-particularly the diffuse positivity for PAX8 and WT1-establishing a definitive diagnosis necessitated a rigorous, exclusion-based approach. After excluding primary pulmonary or thyroid malignancies via the absence of TTF-1 and Tg expression (15), the differential diagnosis focused heavily on germ cell tumors. Because the patient was a middle-aged man and the anterior mediastinum is a common site for extragonadal germ cell tumors, normal serum tumor markers (AFP and HCG) alone were insufficient for exclusion. In this context, the negative expression of SALL4, a highly sensitive marker for germ cell tumors, was of decisive importance in ruling out malignancies such as seminoma and yolk sac tumor (16). Regarding the concern for mesothelioma raised by WT1 positivity, the focal positivity for calretinin might have added to diagnostic confusion; however, complete negativity for D2-40 was crucial in excluding this entity. Furthermore, the tumor's location within the thymic bed, its well-circumscribed growth with a pseudocapsular appearance, and the absence of pleural invasion strongly argued against primary mediastinal mesothelioma (17). Finally, negative CD99 expression helped exclude Ewing sarcoma/primitive neuroectodermal tumor and lymphoma (18). Ultimately, despite the lack of traditional thymic markers (CD5/CD117), the rigorous immunohistochemical exclusion of metastatic origins, together with the typical anterior mediastinal location and the identification of residual atrophic thymic tissue, strongly supported a diagnosis of primary thymic PAT. Of note, the Ki-67 proliferation index of ~10% indicated relatively low proliferative activity, consistent with the early Masaoka-Koga stage I classification and the indolent clinical behavior observed in the present case (8).

From an etiologic and pathogenetic perspective, the present case provides two intriguing insights. Regarding histogenesis, the cystic and solid architecture of the tumor, alongside the surrounding atrophic thymic tissue, supports the 'cyst-adenocarcinoma sequence' hypothesis, which posits that malignant transformation arises from thymic cyst epithelium or microscopic thymic epithelial nests (3,19). Furthermore, the patient had a >10-year history of RA. Autoimmune diseases are often associated with follicular hyperplasia of the thymus and alterations in the local microenvironment (20). Although the specific details of the patient's long-term medication regimen are unavailable-limiting our ability to evaluate the direct impact of potential drug-induced immunosuppression-patients with RA are frequently exposed to immunosuppressive therapies. It is plausible that chronic immune dysregulation and impaired immune surveillance created a permissive microenvironment for the development of this rare neoplasm (21). While direct evidence is lacking in this specific instance, this clinical context should not be overlooked when considering potential mechanisms of tumorigenesis. At the molecular level, the absence of *CDKN2A* deletion and *BRAF* V600E mutation distinguishes this tumor from highly aggressive thymic carcinomas and certain thyroid carcinomas, suggesting that thymic PAT may follow a distinct, relatively indolent molecular evolutionary pathway.

With respect to treatment and prognosis, complete surgical resection with negative margins (R0 resection) remains the cornerstone for achieving long-term disease-free survival in early-stage disease (22). In cystic or cystic and solid lesions, meticulous intraoperative technique to prevent the spillage of cystic contents-the so-called 'no-touch' technique-is critical to reduce the risk of pleural seeding and subsequent metastatic implantation. In the present patient, complete resection was achieved via VATS, and the tumor was staged as Masaoka-Koga stage I. No adjuvant radiotherapy or chemotherapy was administered, and no recurrence was observed during the 6-month follow-up. Although the short follow-up period is a limitation, the favorable short-term outcome aligns with previous reports indicating a good prognosis following the complete resection of early-stage thymic adenocarcinoma.

In summary, the present case strongly illustrates the substantial radiological and immunophenotypical heterogeneity of thymic adenocarcinoma. It underscores that pathologists should not prematurely exclude a primary thymic origin simply due to CD5/CD117 negativity or the atypical

Table I. Clinicopathological, immunophenotypic, and molecular features of primary thymic papillary adenocarcinoma.

Author	Patient [age (years)/sex]	Tumor size (cm)	Associated lesions	Key IHC features	Molecular/genetic	Remarks/outcome	(Refs.)
Matsuno *et al*	70/M	8.0	Type A thymoma (spindle cell)	CEA$^+$, Leu$^-$, M1$^+$, Ber$^-$, EP4$^+$, CD5$^-$	-	Alive with disease (1 year)	(23)
Matsuno *et al*	69/F	5.0	Type A thymoma	Calretinin$^+$, CD5$^-$	-	-	(23)
Matsuno *et al*	61/F	10.0	Type A thymoma	CD5$^+$ (focal), Calretinin$^+$ (focal)	-	Died of other cause (7 months)	(23)
Matsuno *et al*	56/M	3.5	None	High grade atypia	-	NED (5 years)	(23)
Zaitlin *et al*	51/F	12.0	Thymic cyst	-	-	Recurrence due to cyst spillage; died (26 months)	(7)
Yoshino *et al*	29/F	5.5	Type A thymoma (mixed)	CD5$^-$, TTF-1$^-$, Tg$^-$, Ber$^-$, EP4$^+$	-	Rare CD5-negative case	(4)
Morikawa *et al*	68/F	4.0	Thymic cyst and Type A thymoma	CD5$^-$, TTF-1$^-$, Tg$^-$, Calretinin$^+$	-	Alive without recurrence (15 months)	(19)
Hosaka *et al*	36/M	2.2	Type AB thymoma (separate nodule)	CD5$^-$, CD117$^-$, TTF-1$^-$, Foxn1$^-$	-	Long-term survival (11 years)	(24)
Furtado *et al*	44/M	3.5	Residual thymic tissue	CD5$^+$ (focal), TTF-1$^-$, Tg$^-$	-	Alive with disease (24 months)	(5)
Weissferdt and Moran	22/F	7.0	Multilocular thymic cyst	CD5$^+$ (diffuse), CK7$^+$ (focal), p63$^+$	-	Alive with disease (13 months)	(25)
Oka *et al*	84/F	4.5	Type A thymoma (separate nodule)	CD5$^+$, MUC1$^+$, p63$^+$, TTF-1$^-$	-	VATS resection; Good prognosis	(3)
Zheng *et al*	53/F	3.0	Type A thymoma (separate) and lung minimally invasive adenocarcinoma	CD5$^+$, CD117$^+$, TTF-1$^+$ (focal)	KMT2A, ARID1A, CTCF mutations	Rare TTF-1 positive case	(26)
Yorozuya *et al*	50/F	4.2	None	TTF-1$^+$, CK7$^+$, CD5$^-$, Tg$^-$	BRAF V600E mutation	Rare BRAF mutation and TTF-1 positivity	(27)
Current case	48/M	4.2	Atrophic thymus/cystic changes	CD5$^-$, CD117$^-$, PAX8$^+$, WT1$^+$	BRAF wild-type, CDKN2A wild-type	VATS resection, stage I, NED (6 months)	-

CEA, carcinoembryonic antigen; Leu-M1, CD15; Ber-EP4, epithelial cell adhesion molecule; TTF-1, thyroid transcription factor-1; Tg, thyroglobulin; MUC1, mucin 1; CK, cytokeratin; NED, no evidence of disease; MIA, minimally invasive adenocarcinoma; KMT2A, lysine methyltransferase 2A; ARID1A, AT-rich interaction domain 1A; CTCF, CCCTC-binding factor; CDKN2A, cyclin-dependent kinase inhibitor 2A; PAX8, paired box gene 8; WT1, Wilms tumor 1; VATS, video-assisted thoracoscopic surgery.

combination of PAX8 and WT1 positivity. Comprehensive clinical and radiological correlation, broad and rigorously interpreted immunohistochemical panels (encompassing cytokeratin profiles and germ cell markers), and attention to the background of autoimmune disease are all essential for preventing misdiagnosis and underdiagnosis.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WW and DZ conceived and designed the study. DZ, CW, JG and TZ collected and analyzed the clinical, imaging and pathological data. DZ interpreted the data and drafted the manuscript. WW supervised the study and revised the manuscript critically for important intellectual content. CW and DZ contributed to manuscript review, revision and improvements to the English language. DZ and WW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of Shiyan Taihe Hospital granted a waiver of informed consent (approval no. 2026KS99) specifically for the retrospective access and review of the patient's medical records.

Patient consent for publication

A waiver was granted by the Ethics Committee for the retrospective data review, and this waiver did not apply to publication. Therefore, a separate, specific written informed consent was obtained directly from the patient for the publication of this case report and any accompanying clinical images.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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