

An endobronchial-invading clear cell carcinoma of the thymus: A rare case report

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Abstract

Background: Clear cell carcinoma of the thymus (CCCT) is a high-grade and exceptionally rare subtype of thymic carcinoma, accounting for approximately 3% of thymic carcinomas.

Objective: We report a case of CCCT with endobronchial invasion, a rarely documented presentation.

Results: A 50-year-old man presented with progressive dyspnea, hoarseness, hemoptysis, and substantial weight loss over one year. Physical examination revealed tachycardia, tachypnea, and reduced oxygen saturation. Chest radiography demonstrated widening of the superior mediastinum. Contrast-enhanced computed tomography showed a heterogeneous, lobulated mass encasing the superior vena cava and narrowing the bronchial lumen over a 2.5-cm segment above the carina. Bronchoscopy revealed an infiltrative, friable, and easily bleeding mass that nearly obstructed the distal trachea. Histopathologic examination demonstrated a lobulated tumor with dense fibrous stroma, lymphocytic infiltration, and cells with abundant clear cytoplasm, findings consistent with CCCT. The diagnosis was established by integrating the clinical, radiologic, and histopathologic findings. Immunohistochemical analysis and tumor-marker testing were not performed, representing an important diagnostic limitation. The endobronchial invasion extended beyond the typical local invasion pattern described by the International Thymic Malignancy Interest Group, suggesting an unusually aggressive tumor behavior.

Conclusion: This case highlights the diagnostic challenges associated with CCCT. Endobronchial invasion may represent a rare manifestation of this tumor. A complete diagnostic evaluation, including immunohistochemistry and tumor-marker testing, is essential for future cases.

Keywords: thymic carcinoma; clear cell carcinoma; endobronchial invasion; mediastinal tumor; case report

Introduction

Clear cell carcinoma of the thymus (CCCT) is a high-grade and exceptionally rare subtype of thymic carcinoma. The 2021 World Health Organization Classification of Thoracic Tumours recognizes CCCT as a distinct thymic carcinoma subtype, alongside micronodular thymic carcinoma and thymic sebaceous carcinoma. The term “clear cell” refers to individual or grouped tumor cells containing abundant glycogen and surrounded by collagen-rich stroma.¹ Histologically, CCCT is characterized by marked cytologic atypia, increased proliferative activity, and an absence of immature T lymphocytes. This tumor was first described as a distinct pathologic entity by Wolfe et al. in 1983 and accounts for approximately 3% of thymic carcinomas.^{2,3}

Clear cell carcinoma most commonly occurs as a primary tumor of the kidney or ovary. However, thymic clear cell carcinoma may resemble renal clear cell carcinoma or arise from clear cell changes in a well-differentiated

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squamous cell carcinoma.⁴ Although these tumors share similar histopathologic features, they differ in their primary sites, genetic alterations, and biomarker profiles.^{5,6}

Imaging plays an important role in the initial evaluation and staging of mediastinal masses, particularly thymomas and thymic carcinomas, by identifying local invasion and distant metastases.⁷ However, imaging cannot reliably distinguish the clear cell subtype of thymic carcinoma, despite the potential importance of this distinction for treatment planning and prognosis. Histopathologic examination therefore remains essential for classifying the tumor subtype, while immunohistochemistry helps confirm thymic origin and exclude metastatic clear cell carcinoma from other sites.^{3,8} This diagnostic complexity presents a significant challenge in the evaluation of CCCT.

We report a rare case of CCCT with endobronchial invasion in a 50-year-old man, emphasizing the radiologic and histopathologic approach to diagnosis. Although several reviews^{2,3} have described this disease this case contributes to the limited literature on CCCT and may improve understanding of its clinical behavior and diagnostic characteristics.

Case Report

A 50-year-old male presented to the emergency department with worsening shortness of breath over the past 7 days. Patient complained of hoarseness of voice that began 3 months ago. Additionally, the patient reported occasional hemoptysis over the past month, accompanied by a weight loss of 10 kg over the last year. The patient had no prior history of malignancy, autoimmune diseases such as myasthenia gravis, or significant family history. He reported smoking history since high school, with no history of specific medication.

On physical examination, there was increased respiratory rate and tachycardia, also decreased in saturation. Additional breath sounds such as rhonchi or rales were not found. There were no signs of plethora and collateral vein dilatation, and palpable mass in the neck or chest was not found.

A chest X-ray (Figure 1) was first performed, revealed a widening of the superior mediastinum on the right side. There were no abnormalities in the lungs or heart. Further evaluation with a contrast-enhanced CT scan of the thorax (Figure 2) showed a lobulated mass with necrotic components in the superior mediastinum on the right side, measuring 5 x 6.28 x 6.8 cm. The mass encircled and infiltrated the superior vena cava, causing dilatation of its superficial branches. It also invaded the bronchi, narrowing the lumen over a 2.5 cm segment above the carina and displacing surrounding structures. The investigation was extended to bronchoscopy. Histopathological examination of biopsy was performed for further evaluation.

Further evaluation using contrast-enhancement chest CT Scan (Figure 2) demonstrating presence of a heterogeneous, lobulated solid mass measuring 5 x 6.28 x 6.8 cm containing necrotic components within its structure. The mass is observed to encircle and infiltrate the superior vena cava, resulting in significant dilatation of its superficial branches. Additionally, the mass invades the bronchi, causing a notable lumen narrowing over a 2.5 cm segment above the carina while exerting pressure on and displacing adjacent anatomical structures.

The investigation was extended to bronchoscopy examination. Figure 3 showed the finding, illustrates an infiltrative mass characterized by its irregular surface and tendency to bleed easily. It extends to nearly completely obstruct the distal one-third of the trachea, significantly impairing the airway and potentially indicating aggressive local invasion or advanced disease. Biopsy was performed to take the tissue sample for histopathology evaluation.

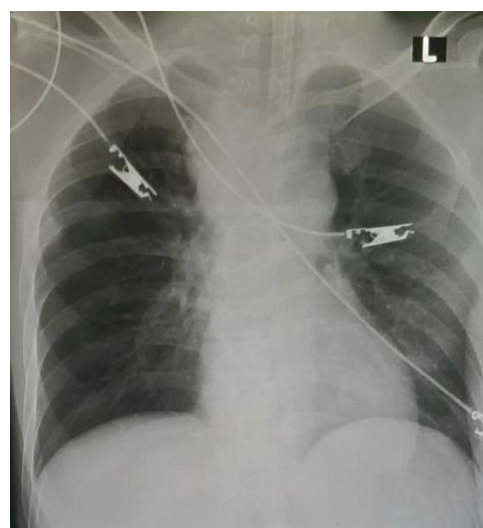


Figure 1. Chest X-ray image in a posteroanterior (PA) projection. A widening of the superior mediastinum was observed on the right side, forming a blunt angle with the lung parenchyma (blue arrow). No abnormalities were observed in the lungs or heart.

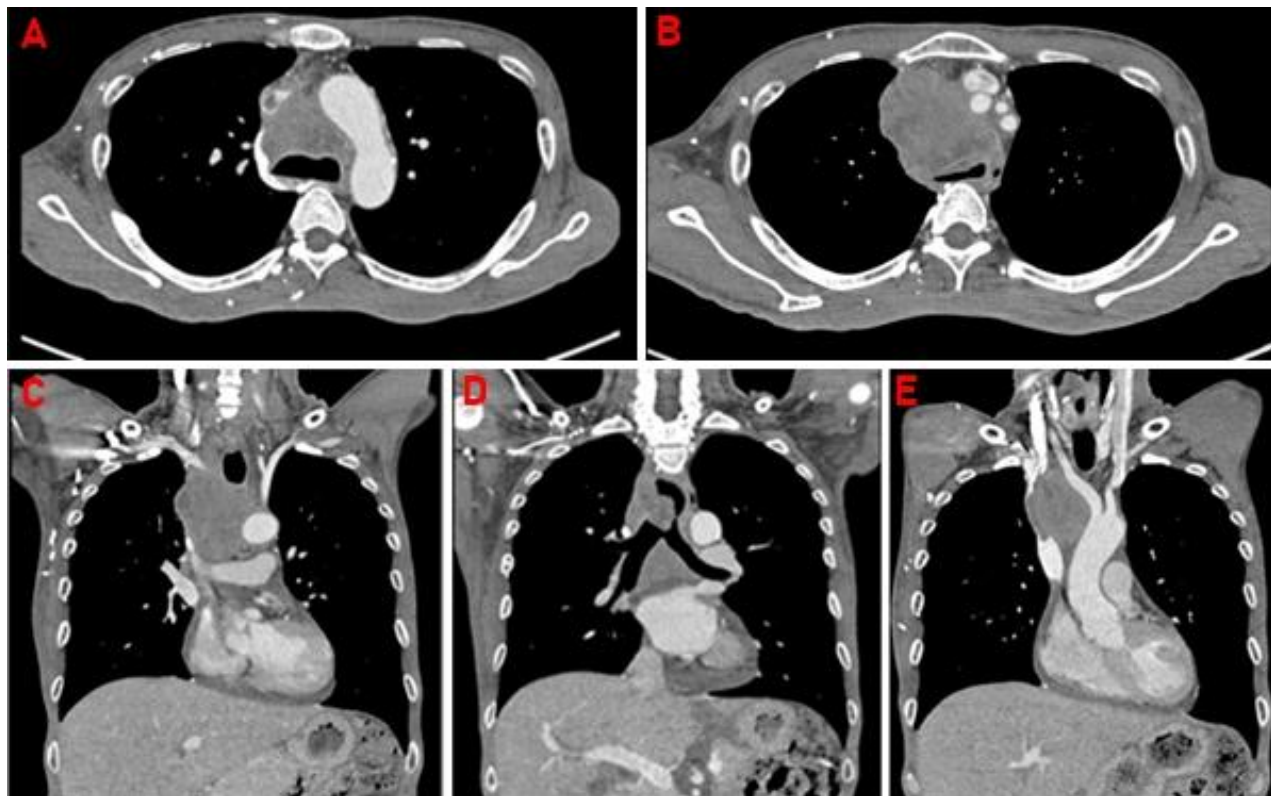


Figure 2. Chest CT Scan with contrast, mediastinal window (A) (B) Axial view (C) (D) (E) Coronal view

The histopathology findings (Figure 4) showed a lobulated architectural pattern in which the structure is divided into distinct lobules separated by a dense fibrous stroma, forming a clear cytoplasm with well-defined borders. Lymphocytes notably infiltrate this stroma, with marked pleomorphism and pathological mitotic figures.

Discussion

Thymic carcinoma is a rare malignancy of the mediastinum originating from thymic epithelial cells.⁹ Fifth edition of WHO classification of Thoracic Tumours (2021) divides thymic neoplasm into thymic epithelial tumours (TETs), mediastinal germ cell tumours, and mesenchymal neoplasm.¹ Compared to others, TETs are the most frequent neoplasm in the anterior mediastinum and usually occur ectopically in the neck. Thymoma (Ts) and thymic carcinomas (TCs), and thymic neuroendocrine neoplasm (NETs) are included into the spectrum of TETs, with totally only 0.23-0.30 cases per 100.000 people per year, especially peaked between 4th and 6th decades.¹⁰ Thymoma is the most common primary anterior mediastinal mass, while thymic carcinoma is rarer, but much more likely to spread.¹¹ Thymic carcinoma represents approximately 20% (17-22%) of TETs, and can be associated with increased parathyroid hormone, hypercalcemia, or pulmonary sarcoidosis.¹²



Figure 3. Bronchoscopy examination

Before clear cell carcinoma was added into the subtype, the 2015 WHO classification for tumors of the lung, pleura, thymus, and heart, TC recognizes 11 subtypes: squamous cell, mucoepidermoid, basaloid, sarcomatoid, lymphoepithelioma-like papillary, clear cell, carcinoma with t(15;19) translocation, undifferentiated carcinoma, papillary and nonpapillary adenocarcinomas, and neuroendocrine tumors (carcinoid, atypical carcinoid, and small and large cell neuroendocrine carcinomas). Of these, however, only squamous cell carcinomas (TSCCs), lymphoepithelioma-like carcinomas, and the neuroendocrine tumors are more common.¹ Clear cell carcinoma thymus is even rarer than other subtype, with only less than 20 reports since its first report in 1983.⁶

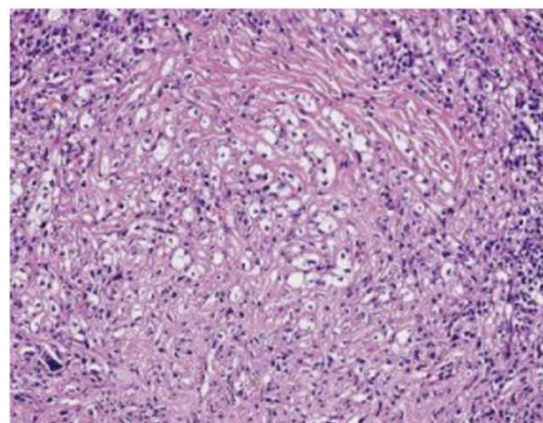


Figure 4. Histopathology examination in Hematoxylin-Eosin (H&E) staining

Thymoma and TCs is not a disease of young adult, the incidence peaks in the 7th decade, or there is a variation between 45 to 55 years. While sex has no influence on the disease. Due to the lack of evidence and reported data, there are no environmental exposure such as tobacco, diet, or alcohol. While another example from clear cell carcinoma of the lung, older patient age and smoking history were well-known as the risk factors of Squamous cell carcinoma with clear cell changes.

Pathogenesis of TC is known to begin from overexpression or mutation of some receptors or their ligands, for example epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (Her2), c-kit, vascular endothelial growth factor receptor (VEGFR), Kirstenrat sarcoma viral oncogene homolog (Kras), insulin-like growth factor 1 receptor (IGF-1R), and platelet-derived growth factor receptor (PDGFR).¹³ When overexpressed, these oncogenes influence tumorigenesis, including promotion of angiogenesis, inhibition of apoptosis, tumor invasion, and increased metastatic rates. TCs also bear the highest TMB (tumor metastatic burden), by showing upregulation of oncogenes and downregulation of onco-suppressors (mainly TP53).^{10,13} While still unclear, tumors with clear cell features have consistent molecular alteration in EWSR1 translocation, such as clear cell carcinoma of the lung¹⁴, clear cell sarcoma¹⁵, clear cell carcinoma of salivary gland¹⁶. Whether EWSR1 translocation present in CCCT remains to be further investigated and was not evaluated in present case.

Mediastinal masses have various radiological and histopathological findings. Radiological imaging is important to assess the site of the mass and the affected organ or tissue first. It plays a pivotal role in confirming the diagnosis, evaluating the efficacy of administered therapeutic interventions, and guiding meticulous treatment planning.¹⁷ In cases of TCs, thoracic radiographs frequently demonstrate a characteristic widening of the superior mediastinum, a radiological hallmark suggestive of a mediastinal mass.⁷ However, while chest radiographs provide valuable initial diagnostic clues, further clarification and detailed evaluation of these findings are essential.

In this regard, contrast-enhanced computed tomography (CT) of the thorax emerges as a critical imaging modality, as it facilitates precise identification of the tumor's anatomical location, internal density, and degree of involvement with adjacent structures, including vital organs.¹⁷ Contrast-enhanced CT is the choice for imaging modality for thymic masses due to its high spatial resolution, accessibility, and ability to assess site of tumor, morphology, internal density, and relationship to adjacent structure.^{7,18} In TC, specifically, CT demonstrates a large, poorly marginated prevascular mass with heterogeneous enhancement reflecting areas of internal necrosis, hemorrhage, and cystic change. Lymphadenopathy, pericardial or pleural effusion, and invasion into adjacent vascular structure often accompany.^{7,19} In our patient, contrast-enhanced CT found a heterogenous lobulated mass measuring 5 x 6.26 x 6.8 cm with necrotic components, encircling the SVC and narrowing the bronchial lumen. The findings consistent with high-grade thymic malignancy as described in the literature.

While CT remains the primary modality for staging and evaluating vascular involvement, MRI offers complementary value in specific scenario. Particularly, in distinguishing cystic from solid components, evaluating

subtle soft tissue invasion, and characterizing cardiac involvement due to its superior contrast resolution.^{7,17,18} A comparative study found that while CT and MRI demonstrated comparable overall sensitivity of 100% for thymic masses, MRI demonstrated higher specificity for detecting thymomas and thymic cysts, whereas CT showed superior diagnostic accuracy for TC specifically, supporting its role as the first-line modality in suspected malignant case.^{19,20} In present case, CT findings were sufficient to characterize the extent of local invasion without the need for MRI. However, CT alone could not definitively confirm the bronchial involvement. It provides information regarding tumor size, location, and its spatial involvement to adjacent mediastinal structures including extrinsic bronchial compression or displacement. However, it cannot distinguish the extrinsic compression from true transmural or endobronchial invasion, nor assess the intraluminal extent. Bronchoscopy complements CT by enabling direct visualization of the bronchial mucosa and lumen, in which and infiltrating and easily-bleed mass.^{17,18} The integration of both CT and bronchoscopy is therefore essential in the evaluation of mediastinal masses with suspected airway involvement, as it directly influences tumor staging and guides treatment planning.

Clinically, TC often demonstrates radial invasion into the thymus and surrounding adipose tissue and a propensity for widespread metastasis.¹⁸ Our patient presented with progressive dyspnea, hoarseness, hemoptysis, and significant weight loss. These symptoms are predominantly driven by local invasion of adjacent structure. This finding is consistent with the aggressive local invasion characteristic of thymic carcinoma as described in the literature. However, CCCT has rarely been reported to invade the endobronchial.^{2,3,6,21} Instead, endobronchial invasion has been reported in invasive thymoma, which also a rare occurrence.²² The International Thymic Malignancy Interest Group (ITMIG) divide the thymic neoplasm invasion and metastases into 4 stages. The local invasion site includes the thymic capsule, fatty tissue, mediastinal pleura and pericardium, great vessels, or surrounding nodal invasion.¹¹ Notably, endobronchial invasion is not included among the typical local invasion sites defined by ITMIG. Based on TNM staging system for thymic tumors adopted in the 8th edition of AJCC classification, SVC encasement corresponds to at least T3 disease. While in Masaoka-Koga staging system, bronchial involvement may suggest a macroscopic invasion into neighboring organ which included in stage III. This further corroborates the unusually aggressive local invasion pattern observed in this case.

This aggressive pattern should be potentially influencing the choice of therapeutic modality or prognostic consideration. Surgery is the main treatment of thymic tumors. According to the TNM system, thymectomy is the standard surgical procedure for stage I and II thymic tumors. While in stage III and IV, there is no place for minimally invasive procedures. Thymic tumors with surrounding tissue involvement as presented in this case need complete thymectomy with surrounding fatty tissue or mediastinal pleura resection may be considered. However, radicality of the resection through the endobronchial is still a big dilemma to be made, considering the challenge in airway reconstruction and the need to maintain adequate oxygenation. If the tumor is unresectable, induction chemotherapy with radiotherapy may be considered to do.²³

Radiographically, there is still not much literature that more specifically differentiates clear cell carcinoma of the mediastinum from other mediastinal carcinomas. To differentiate the subtype of TC, histology examination remains the cornerstone of diagnosis. Histologically, around 70% of thymic carcinomas are of the squamous cell carcinoma subtype with tumor infiltrating lymphocytes. While non-squamous TCs represent only minority of TCs with different types of variety, i.e. basaloid, sarcomatoid, clear cell, lymphoepithelioma-like or glandular features.¹² We found similar morphology showing lobulated architecture in histopathological slide using H&E staining showed in many reports, usually separated by a dense fibrous stroma with lymphocyte infiltration.² Significantly, Dai et al.³ in their case report also found similar lobulated architecture composed of undifferentiated clear cell with the density of fibrous stroma, but with penetration to adipose tissue. Additionally, H&E staining revealed cells with abundant clear cytoplasm and distinct cell borders, consistent with the clear cell morphology that defines this entity.

As mentioned before, clear cell carcinoma might occur in other organs, including the kidney, ovary, salivary gland, parathyroid adenoma or carcinoma, thymoma with clear cell components, mediastinal seminoma.² Therefore, those differential diagnoses should be excluded. This is the important role of IHC, where the specific

biomarker from the staining could help to distinguish the different characteristics of clear cell origin. For example, clear cell Renal Cell Carcinoma (ccRCC) has important markers such as PAX8 and CAIX.²⁴ While in CCCT, a literature review found strong diffuse positivity in the AE1/AE3, EMA, CK18, and partial positivity in CD10, PAX8, and vimentin.² A positive CK AE/AE3 also found in IHC staining from biopsy specimen.²¹ Tumor marker such as B-HCG and AFP may be needed to rule out other mediastinal neoplasm, such as mediastinal germ cell tumor and neuroendocrine tumor.⁹ The absence of myasthenia gravis history and symptoms in this patient is consistent with the diagnosis of TC, as MG is a well-recognized paraneoplastic manifestation that occurs in approximately 30% of thymoma patients.¹⁷ This distinction represents an important differentiation clinical feature between those two entities. Further workup including acetylcholine receptor antibody (AchR-Ab) and titin antibody (Titin-Ab) may be utilized to evaluate MG, with are predominantly positive in thymoma rather than in thymic carcinoma.³

While IHC and other tumor markers examinations would have been valuable in supporting the diagnosis, these could not be performed in this case due to two primary constraints: the limited amount of biopsy tissue obtained via bronchoscopy, and financial limitations imposed by the national health insurance coverage ceiling. These factors represent a significant diagnostic limitation particularly in confirming thymic carcinoma subtypes and excluding other mediastinal malignancy. Nevertheless, the diagnosis of CCCT was established based on the integration of the clinical presentation, radiology findings, and histopathology morphology on H&E staining. The absence of extra-thoracic symptoms, prior malignancy history, and the characteristic histopathological architecture supported a primary thymic origin rather than metastatic disease.

Conclusion

Clear cell carcinoma of the thymus is an exceptionally rare and aggressive malignancy, representing one of the least documented subtypes of thymic carcinoma. This case demonstrates the typical aggressive behavior of CCCT, presenting dyspnea, hoarseness, hemoptysis, and weight loss due to extensive local invasion. A notable feature is endobronchial invasion, which is not commonly reported in CCCT and extends beyond the typical local invasion pattern defined before. This case contributes to the limited but growing literature of CCCT. Integrating clinical findings and performing complete diagnosis workups may help to solve diagnosis challenge of this rare case. The absence of IHC and tumor markers in this case represents a significant diagnosis limitation that should be addressed in future reports.

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