



## **Original Article**

### **Multidisciplinary Management of Advanced Thymoma: A Case Study of a 47-Year-Old Female and Implications for Future Research**

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#### **ABSTRACT**

**Objective:** By leveraging insights from the case and subsequent discussions, we aim to improve our understanding of thymic malignancies and promote further research and collaboration.

**Methods:** A 47-year-old female, J.D., who presented with a history of easy fatigability, bilateral extremity weakness, and shortness of breath diagnosed with advanced thymoma and metastases, received a multidisciplinary evaluation. Doctors considered surgery, radiation, and systemic therapy, tailoring the approach based on tumor stage and patient needs. The team monitored response through examinations and tests, planning follow-ups to track progress.

**Results:** Diagnosing thymoma involves tissue examination and genetic testing, with treatment varying by cancer stage. In this case, the initial evaluation revealed controlled hypertension and a history of four pregnancies. Imaging scans found a mass in the chest and suspicious nodules in the liver and abdomen. A biopsy confirmed thymoma with no signs of spread beyond the initial tumor sites. Surgery is a key treatment option, with minimally invasive techniques being explored for faster recovery. Early-stage surgery may not require radiation, but advanced tumors benefit to systemic therapy to eliminate microscopic disease and improve survival.

A chemotherapy regimen was well-tolerated with minimal side effects, and surveillance CT scans were requested to monitor the response to treatment. While the initial treatment was successful, ongoing challenges exist due to the limitations of systemic therapy and the potential for residual disease. Treating metastatic thymoma after chemotherapy remains a challenge. Some doctors consider pembrolizumab for patients unable to tolerate other treatments, but more research is needed for this complex cancer. Overall, while the treatment itself showed promise, the limitations of current therapies and the potential for residual disease continue to pose challenges in managing thymoma.

**Conclusion:** This case of thymoma highlights the complexities of diagnosis and treatment for this rare cancer. While initial treatment showed promise, with well-tolerated chemotherapy and careful monitoring, the management of thymoma continues to present challenges. The potential for residual disease and limitations of current systemic therapies underscore the need for ongoing research and personalized treatment approaches. As medical science advances, particularly in areas such as immunotherapy, there is hope for improved outcomes and quality of life for patients with thymoma.

**Keywords:** Advanced thymoma, multidisciplinary, metastatic disease, thymic malignancies

## INTRODUCTION

Thymomas, rare tumors from the thymic epithelium, pose significant challenges in clinical management due to their variable clinical presentation and complex treatment considerations. We present the clinical course of a 47-year-old female, J.D., who presented with a history of easy fatigability, weakness of bilateral extremities, and shortness of breath. Initial evaluation revealed a mediastinal mass, prompting further investigation through a comprehensive diagnostic workup. The significance of this case lies in its complexity, as the patient was diagnosed with advanced-stage thymoma accompanied by lung and liver metastasis, along with a concurrent ovarian new growth. This unique presentation underscores the intricacies of managing rare malignancies, necessitating a multidisciplinary approach and personalized treatment strategies.

The rationale for presenting this case stems from highlighting the diagnostic challenges, treatment considerations, and emerging therapeutic modalities in advanced thymomas. By synthesizing insights from the initial case presentation and the opening discussions in the forum, we aim to contribute to the understanding of thymic malignancies and stimulate further research and collaborative efforts in this field.

The case presentation provides a comprehensive understanding of the clinical, pathological, and therapeutic aspects of managing advanced-stage thymomas and insights into emerging biomarkers and genetic syndromes associated with thymic malignancies. The learning objectives that readers should gain from the discussion are the following:

1. Gain insight into the diagnostic challenges associated with rare malignancies like advanced-stage thymomas.
2. Understand the importance of a multidisciplinary approach in managing complex cases involving thymic malignancies.
3. Explore the nuances of treatment selection and personalized therapeutic strategies for advanced thymomas.
4. Appreciate the significance of integrating diverse perspectives and expertise in optimizing patient outcomes in rare malignancies.

## METHODS

This case presentation is of a patient diagnosed with advanced-stage thymoma accompanied by lung and liver metastasis, along with a concurrent ovarian new growth. A multidisciplinary forum discussion framework involving experts from pathology, radiology, medical oncology, and surgery analyzes this case.

### Participants

The patient included in this case report is a 47-year-old female, denoted as J.D., who presented with symptoms suggestive of advanced-stage thymoma. The case presentation then involves input from experts across various medical specialties, contributing to a comprehensive understanding of the clinical management of rare malignancies.

### Data Collection and Analysis

The presenter collected data for this case presentation from the patient's medical records, which included diagnostic imaging studies, pathological reports, and treatment records.

### Diagnostic Workup

The diagnostic process began with a chest X-ray followed by a subsequent investigation through a chest CT scan and biopsy. Further imaging modalities employed included cranial and whole abdominal CT scans, transvaginal ultrasound, 2D echo with Doppler, bone scintigraphy, and

pulmonary function tests. Laboratory investigations encompassed anti-acetylcholine receptor (IgG), CA 125, CA 19-9, and CEA levels. Subsequent histopathological examination supported by immunohistochemistry confirmed the diagnosis of thymoma. The radiology team performed imaging studies to investigate the spread of cancer to other organs. These studies included a cranial CT scan and a 2D echocardiogram with Doppler ultrasound.

### **Treatment Approach**

A multidisciplinary team managed the patient's case, involving medical oncology, radiation oncology, and surgical specialists. They discussed treatment options, including surgery, radiation therapy, and systemic therapy. The multidisciplinary team considered surgical resection for cases where the disease could be removed entirely (resectable disease). They indicated radiation therapy as a possible treatment approach for locally advanced or unresectable cancers. Radiation therapy could be used in different settings: adjuvant (following surgery), neoadjuvant (before surgery), or definitive (as the primary treatment).

### **Response to Treatment**

The multidisciplinary team monitored the patient's response to treatment through clinical evaluations, imaging studies, and laboratory investigations. They conducted objective response assessments to evaluate tumor regression, symptom relief, and treatment-related adverse events. The team members scheduled follow-up appointments to actively assess the treatment's effectiveness, monitor for disease progression, and evaluate patient outcomes.

## **RESULTS**

### **Patient Selection and Clinical Presentation**

A 47-year-old female, J.D., with a history of easy fatigability, weakness of bilateral extremities, and shortness of breath, presented with symptoms suggestive of advanced-stage thymoma. Initial evaluation included a thorough medical assessment, family history review, and physical examination. The patient's medical history revealed controlled hypertension, and obstetric-gynecologic history indicated G4P4 status, with the last menstrual period in November 2023. There was no history of smoking or alcohol consumption.

### **Diagnostic Results**

A chest CT scan identified a well-defined, enhancing soft tissue mass measuring 4.5 x 6.4 x 8.4 cm in the right anterior mediastinum. Further imaging detected hepatic nodules and a solid mass in the right adnexal region, suggesting metastasis. A tissue biopsy was performed to confirm the diagnosis.

A tissue biopsy confirmed the diagnosis of thymoma, with immunohistochemistry revealing positive CK and TdT expressions and negative Synaptophysin expression. The histological classification indicated a predominance of spindle and polygonal cells, consistent with thymoma. Additionally, relevant laboratory results included normal levels of the anti-acetylcholine receptor (IgG), CA 125, CA 19-9, and CEA, suggesting no systemic involvement beyond the primary tumor sites.

### **Treatment Outcomes**

A medical oncology fellow administered a chemotherapy regimen for the patient consisting of doxorubicin 50mg/m<sup>2</sup>, cisplatin 50mg/m<sup>2</sup>, and cyclophosphamide 500mg/m<sup>2</sup>, administered every 21 days for six cycles. The patient tolerated the treatment well, and the fellow managed any side effects that arose. The fellow recommended scheduling interval CT scans to monitor the response to chemotherapy.

## Complications

The patient tolerated the treatment well, with minimal complications consisting of grade 1 neutropenia and nausea with significant adverse events reported during therapy. This positive outcome suggests that the treatment regimen was well-tolerated. However, systemic therapy's limited efficacy and residual disease postoperatively pose ongoing challenges in disease management.

## DISCUSSION

The discussants: Pathology (Dr. Grig Misiona), Radiation Oncology (Dr. Angela Tagle), TCVS (Dr. Giovanni Villaruz), Medical Oncology (Dr. Guia Elena Imelda Ladrera)

The presented case of advanced-stage thymoma with lung and liver metastasis, along with a concurrent ovarian new growth, underscores the complexity of managing rare malignancies. The multidisciplinary discussions within the forum provided insights into various perspectives on diagnostic workup, treatment modalities, and therapeutic challenges.

### Pathological Insights

Pathological evaluation, including histological examination and immunohistochemistry, played a crucial role in confirming the diagnosis of thymoma and guiding treatment decisions. The forum discussions highlighted the significance of identifying pathognomonic histologic findings and immunohistochemical markers for accurate diagnosis and classification.

#### **What pathognomonic histologic findings and immunohistochemistry are needed to diagnose thymoma?**

Accurate diagnosis of thymoma involves histological examination and immunohistochemistry (IHC). Histologically, abnormal epithelial cells—spindle or polygonal—are typically observed, guiding classification under the 2021 WHO scheme for thymomas (Types A, AB, B1, B2, B3, and C).<sup>1</sup>

IHC confirms the diagnosis and excludes other conditions. Using cytokeratin verifies epithelial origin, distinguishing neoplastic growth from reactive thymocytes, which are TdT-positive.<sup>1</sup> Marker choice in IHC depends on cell morphology: CD3 and CD20 detect polygonal cells, distinguishing thymoma from lymphoma, while synaptophysin may be used for spindle cells to rule out neuroendocrine tumors.<sup>1</sup>

Diagnosing thymoma requires a comprehensive approach combining tissue analysis with targeted IHC. Cell morphology guides marker selection to ensure accurate differentiation from other potential diagnoses.

#### **What is the difference between lymphoma and thymoma microscopically?**

Distinguishing thymoma from lymphoma in small biopsies poses significant challenges. While these entities can appear similar microscopically, precise diagnosis relies on immunohistochemistry (IHC) analysis.

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Distinguishing thymoma from lymphoma in small biopsies poses significant challenges. While these entities can appear similar microscopically, precise diagnosis relies on immunohistochemistry (IHC) analysis. Histological examination remains the initial step, where pathologists classify the predominant cell type—spindle-shaped or polygonal cells—to guide further investigation. However, due to microscopic similarities, IHC becomes crucial for definitive diagnosis. Markers like CD3 and CD20 are commonly employed based on the predominant cell type (polygonal cells) to differentiate between Thymoma and lymphoma.<sup>1</sup>

**What is the role of NGS in this case?**

Due to thymoma's rarity and classification as an epithelial tumor, Next-Generation Sequencing (NGS) is gaining recognition as a viable diagnostic technique. NGS provides comprehensive genotyping, revealing a wide array of genetic changes in the tumor. This detailed information can help tailor therapy to match the patient's tumor profile. Meta-analyses of NGS studies identify commonly mutated genes like GTF21, TP53, and HRAS, which play roles in thymoma formation and progression.<sup>2</sup>

NGS also assesses tumor mutational burden (TMB). Studies from The Cancer Genome Atlas and Foundation Medicine indicate that thymomas generally exhibit low mutation rates.<sup>3</sup> This low TMB is crucial for determining appropriate treatment strategies. NGS's ability to analyze genetic data and TMB enhances its role in diagnosing thymoma and guiding personalized treatment plans for improved patient outcomes.

Radiation oncology experts emphasized the role of radiation therapy in locally advanced or unresectable thymomas. The radiation therapy team engaged in a detailed discussion regarding the ongoing debate about adjuvant versus neoadjuvant radiation therapy. They also explored the optimal radiation dose and techniques for minimizing toxicity.

**Is radiation involved in locally advanced diseases?**

Although surgery is primary for thymoma, radiation therapy (RT) is crucial, especially for locally advanced disease. RT can optimize outcomes before, during, or after surgery. In the adjuvant setting, RT is generally not recommended after complete surgical removal (R0) of early-stage Thymoma (Masaoka-Koga Stage I with no capsular invasion). However, for tumors invading the capsule (Masaoka-Koga Stage II to IV), adjuvant RT is considered to eliminate microscopic disease post-surgery, aiming to improve local control and long-term survival.<sup>4</sup> The radiation therapy team selectively chooses neoadjuvant RT for patients with large or locally advanced tumors that cannot be immediately removed (resected). It helps shrink tumors for easier surgical removal. Definitive RT offers an alternative for patients ineligible for surgery, delivering a high radiation dose for long-term tumor control or potential cure.

**What is the role of adjuvant radiation therapy in thymoma management?**

Adjuvant radiation therapy (RT) plays a complex role in thymoma treatment post-surgery, depending on the surgical removal extent (R status) and disease stage. For completely resected early-stage thymomas (Masaoka-Koga Stage I with no capsular invasion), adjuvant RT is generally not recommended due to a shallow recurrence risk.<sup>4</sup>

However, the decision on adjuvant RT is nuanced for tumors with capsule invasion (Masaoka-Koga Stage II to IV). Evidence of its efficacy is mixed.<sup>5,6</sup> While some studies suggest it helps control the tumor site post-surgery, others question its impact on overall survival.

Adjuvant RT becomes crucial for patients with incomplete tumor removal (R1 or R2). Studies show that postoperative radiation therapy (RT) significantly reduces the risk of tumor recurrence in the chest cavity of these patients. Overall, the decision to use adjuvant RT after thymoma surgery hinges on resection level and disease stage. While its benefit in R0 resections for Stage I Thymoma remains debated, adjuvant RT is vital for preventing local recurrence in incomplete resections (R1/R2).

**Does neoadjuvant therapy for thymoma optimize surgical outcomes?**

Neoadjuvant therapy, administered before surgery, is valuable for managing thymoma in specific situations. It aims to shrink tumors, making surgical removal (R0 resection) easier and improving long-term results. Additionally, it enhances resectability by shrinking large or

advanced tumors to a size that allows for safer, more complete removal, especially for borderline resectable or initially unresectable tumors. Furthermore, neoadjuvant therapy helps reduce tumor spread during surgery by shrinking the tumor and reducing the number of viable cancer cells, thereby mitigating the risk of unintentionally spreading cancer cells.

Research shows promising results, particularly for Stage III Thymoma, with R0 resection rates ranging from 53% to 75% after neoadjuvant treatment, highlighting its potential benefits for specific patients.

### **Is radiation therapy a definitive treatment for unresectable thymoma?**

When surgery is not possible due to unresectable illness or patient comorbidities, radiation therapy (RT) becomes a definitive treatment for thymoma. This strategy aims to provide substantial radiation to achieve long-term tumor control or a complete cure.

Studies support the efficacy of definitive RT. Arakawa et al. found that 58% of patients with unresectable thymoma survived 1 to 5 years with initial RT.<sup>7</sup> Ciernik et al. reported an 87% 5-year survival rate for Stage III to IV Thymoma treated with RT alone.<sup>8</sup> Jackson et al. demonstrated a 44% survival rate over ten years for patients with biopsied thymoma who underwent RT.<sup>6</sup>

Due to the rarity of thymoma, most studies on definitive RT are retrospective with small participant numbers, necessitating careful data analysis.<sup>7,8,9</sup>

### **What are the possible side effects after radiation of the anterior mediastinum?**

Radiation therapy is crucial for treating thymoma, especially when surgery is not an option. However, irradiating the anterior mediastinum risks affecting vital organs like the heart, lungs, and esophagus, necessitating careful patient selection and treatment planning.<sup>10</sup>

While radiation can damage nearby structures, most side effects are typically subclinical, meaning they cause no noticeable symptoms. The RTOG/EORTC grading system classifies these toxicities from grade 1 (mild) to grade 5 (fatal). The overall chance of experiencing severe side effects following radiation therapy is reassuringly low at only 5%.

### **How are radiation therapy-related complications minimized?**

Radiation therapy is essential for treating thymoma, especially when surgery is not possible. However, irradiating the anterior mediastinum risks affecting vital organs like the heart, lungs, and esophagus. Therefore, careful patient selection and meticulous treatment planning are crucial.<sup>10</sup>

Modern radiation techniques have significantly reduced complications. Radiotherapists aim to deliver radiation precisely, targeting the tumor while protecting nearby healthy tissues. One essential technique is Intensity-Modulated Radiation Therapy (IMRT), which uses multiple radiation beams with varying intensities to create a precise dose distribution, minimizing exposure to vital organs.<sup>10,11</sup>

Another advancement is 4D Treatment Planning, which accounts for lung and mediastinum movement during respiration, improving treatment for tumors like thymoma. Respiratory Gating delivers radiation during specific breathing phases, typically using the Deep Inspiration Breath Hold (DIBH) technique. DIBH reduces organ and tumor movement, increases the distance between the heart and the target area, and minimizes radiation exposure to healthy tissues.<sup>11</sup>

The radiation therapy team adapted deep inspiration breath-hold (DIBH), a technique initially developed for treating left-sided breast cancer for thymoma therapy. This adaptation allows for optimal lung expansion during radiation therapy, which reduces the radiation dose delivered to critical structures near the lungs. In conclusion, while radiation therapy for anterior mediastinal thymoma poses potential side effects, innovative approaches like IMRT with 4D planning and respiratory gating significantly reduce these risks and improve patient outcomes.

**What is the role of RT in SVC syndrome secondary to thymoma?**

The team carefully weighs the use of radiation therapy for patients with thymoma, especially when considering the potential risk of superior vena cava (SVC) syndrome, a life-threatening condition. A definitive tissue diagnosis is crucial for mild to moderate SVC symptoms (grades 1-3). If the thymoma is operable, surgery is preferred for complete tumor removal and symptom resolution.<sup>12</sup>

For severe, life-threatening symptoms (grade 4), immediate intervention with a venogram and stenting is critical to restore blood flow and alleviate symptoms. Once stabilized, surgery remains the preferred option if the tumor is safely removable.<sup>12</sup>

In advanced cases, treatment focuses on managing cancer spread. For Stage IV thymoma with metastases but no SVC symptoms, systemic therapy targets both the primary tumor and metastases to control disease progression. RT's effectiveness in treating SVC syndrome depends on symptom severity and disease stage. The surgery team prioritizes completely resectable tumors. Emergent stenting takes precedence in emergencies. Systemic therapy is the preferred course of action for advanced, unresectable diseases. The goal is to balance managing SVC symptoms and addressing the thymoma with the most appropriate treatment.

**Surgical Interventions**

Thoracic and cardiovascular surgeons debated the feasibility and benefits of surgical resection, including debulking surgery and metastasectomy. Minimally invasive surgical approaches were favored for selected patients, considering their potential advantages in recovery and outcomes.

**What is the recommended approach for a biopsy of an anterior mediastinal mass to minimize the risk of tumor seeding to pleural space?**

Image-guided biopsy, often using CT scan guidance, is preferred for identifying anterior mediastinal masses but poses a risk of tumor seeding along the needle path.<sup>13</sup> To minimize this risk, healthcare professionals prefer using a 23-gauge needle for fine-needle aspiration (FNA) biopsy over a larger 14-gauge needle for core needle biopsy (CNB), as FNA biopsies extract smaller tissue samples, reducing the likelihood of spreading tumor cells.<sup>13,14,15</sup> Needle tract metastases after mediastinal tumor biopsy are rare, estimated at 0.006%.<sup>15</sup> Prioritizing FNA biopsy over CNB whenever possible further reduces this minimal risk.

**Is the patient a candidate for upfront surgery?**

The decision to perform surgery for a thymoma depends on the disease stage. For Stage IV thymoma, indicating distant metastases, upfront surgery to remove the primary tumor is generally not the most appropriate initial treatment. Surgery might be an option for some Stage IV cases, particularly with a limited number of metastases that can be safely removed, ranging from metastasectomy to extrapleural pneumonectomy. However, researchers debate the effectiveness of this approach due to the limited number of retrospective studies on this rare patient population.<sup>16</sup> Given these factors, the focus would likely shift to systemic or radiation therapy, depending on specific considerations and the patient's overall health.

**Is there a role of debulking surgery and metastasectomy in thymic malignancy?**

Surgery is multifaceted in managing thymic malignancies, extending beyond curative intent. Debulking surgery and metastasectomy can manage symptoms and potentially improve outcomes.<sup>16</sup> Debulking surgery involves removing as much tumor tissue as possible, even if complete removal is not achievable. This approach benefits patients with large tumors causing symptoms like difficulty breathing, chest pain, and superior vena cava (SVC) syndrome. However, Fan et al. found no improvement in overall survival or progression-free survival for locally advanced, unresectable Masaoka-Koga Stage III thymomas with debulking surgery.<sup>17</sup>

Debulking surgery may positively affect myasthenia gravis symptoms by reducing antibody production. Metastasectomy removes isolated metastatic lesions after controlling the primary tumor. Surgery is not very effective for treating locally invasive disease, necessitating a multimodal approach with adjuvant and neoadjuvant radiation and chemoradiation. The decision to use debulking surgery or metastasectomy depends on factors like tumor size, metastases, and patient health. These procedures offer valuable tools for managing thymic malignancies by alleviating symptoms and potentially improving prognosis when combined with radiation or systemic therapy.

#### **Is a minimally invasive procedure for thymoma possible?**

Minimally invasive surgery (MIS) has become the preferred approach for treating thymoma when possible, offering advantages over traditional open thoracotomy.<sup>18</sup> Two main MIS procedures are used: Video-Assisted Thoracoscopic Surgery (VATS) and robotic-assisted surgery. MIS offers faster healing, less pain, and shorter hospital stays than open surgery. However, it is only suitable for some patients, with tumor characteristics and surgical expertise being critical determining factors. Surgeons may choose either a thoracic or subxiphoid approach, providing minimally invasive access to the mediastinum.<sup>19</sup> Careful evaluation is crucial to determining its suitability in each case.

#### **Systemic Therapy Options**

Medical oncologists deliberated on the limited efficacy of chemotherapy and targeted therapy in metastatic thymoma. They explored the potential role of immunotherapy, particularly pembrolizumab, in thymic malignancies, highlighting its associated adverse events and challenges in patient selection.

#### **Is there a role for maintenance therapy after 1st line chemotherapy in metastatic disease?**

The lack of clear guidelines for maintenance therapy after first-line chemotherapy in metastatic thymoma exposes a critical gap in our understanding of how to treat this disease. Although no definitive proof supports using maintenance therapy after the first treatment, ongoing research actively investigates its potential benefits. It aims to establish appropriate treatment plans for this specific patient group.

#### **Is there a role for immunotherapy in thymic malignancy in 1st line metastatic setting or subsequent therapy, or as maintenance therapy after chemotherapy?**

Immunotherapy for thymic malignancies is a developing field with promising potential and significant challenges. Medical oncologists consider pembrolizumab as a possible first-line treatment for metastatic thymic cancer patients with low functional capacity, although data for this specific use is limited. However, a phase 2 trial reported a 70% incidence of immune-related adverse events (irAEs) in thymoma patients,<sup>20</sup> necessitating careful patient selection and monitoring.

Conventional treatments for metastatic thymoma show limited efficacy. The optimal cytotoxic combination yields an overall response rate (ORR) of 44%,<sup>21</sup> while paclitaxel and carboplatin have a 20% ORR for thymic cancer.<sup>22</sup> Second-line targeted therapies show even lower response rates.<sup>23</sup>

Pembrolizumab is contraindicated in thymomas due to immune-related side effects.<sup>24</sup> However, PD-1/PD-L1 expression in thymic epithelial tumors suggests a potential target for immunotherapy, with higher expression in more aggressive subtypes.

As a second-line treatment, pembrolizumab shows some effectiveness, with 28.6% and 19.2% response rates for thymoma and thymic carcinoma, respectively.<sup>25</sup> However, the risk of severe irAEs remains significant, occurring in up to 70% of thymoma patients.<sup>24</sup>



While immunotherapy shows potential, particularly considering PD-L1 expression, significant obstacles remain. Careful patient selection and continued research are necessary to enhance treatment approaches and establish safer, more efficient immunotherapy protocols for thymic malignancies.

**Are there emerging biomarkers in the detection and monitoring of treatment response?**

Identifying reliable biomarkers for thymic epithelial tumors (TETs) remains an ongoing pursuit in oncology. These tumors have the potential for early detection and treatment monitoring. However, challenges include their rarity and heterogeneity.

Circulating cell-free DNA (cfDNA) shows promise as a non-invasive biomarker. An Italian study identified higher cfDNA levels in TET patients compared to controls. The study also found elevated cfDNA levels in patients with advanced stages of the disease. However, the study did not find a significant link between cfDNA levels and disease stage or tumor burden.<sup>26</sup> Research in lung cancer suggests cfDNA could potentially serve for early TET detection. However, further research, including more extensive multicenter studies, is needed to validate cfDNA's role as a TET biomarker.

A multi-biomarker approach might help address the challenges posed by TET heterogeneity. While challenges exist due to the rarity and heterogeneity of these tumors, cfDNA and other emerging biomarkers offer hope for improved detection, monitoring, and patient outcomes in TET management.

**Is thymic malignancy related to any genetic syndromes that have a propensity to develop secondary malignancy?**

While thymic malignancies are not typically associated with hereditary cancer syndromes, a limited link with Lynch syndrome (LS) has been reported. LS, an autosomal dominant syndrome, affects 1 in 250 to 1000 individuals and arises from mutations in DNA mismatch repair genes: MSH2, MLH1, MSH6, and PMS2.<sup>27, 28</sup>

LS increases the risk of various cancers, primarily colorectal and endometrial. Case reports suggest a potential association between thymic malignancies and LS, particularly in patients with MLH1 mutations.<sup>27</sup>

Diagnosing Lynch syndrome (LS) involves two main tests: tumor-based and germline testing [28]. For patients with both thymic malignancies and suspicious adnexal masses, medical oncologists recommend further evaluation. This evaluation should include a biopsy to obtain tissue samples and testing to assess mismatch repair (MMR) function or microsatellite instability (MSI-H) status. Germline testing should then be performed. Identifying LS in a patient with thymic malignancy has significant implications for cancer surveillance strategies for both the patient and family members. While the link between thymic malignancies and Lynch syndrome (LS) is not fully understood, new evidence suggests a connection worth investigating further. Comprehensive genetic evaluation is essential in patients with thymic cancers, especially those with additional risk factors or a family history suggestive of LS. This approach can lead to more tailored care and potentially uncover crucial genetic information that benefits the patient and their family in cancer risk assessment and management.

**CONCLUSION**

This case report underscores the importance of interdisciplinary collaboration, ongoing research, and individualized treatment approaches in optimizing outcomes for patients with advanced thymomas. It contributes to our understanding of thymic malignancies and paves the way for future advancements in their management.

The insights gained emphasize the need for tailored patient care, considering specific tumor

characteristics and patient preferences. Ongoing collaboration and research are crucial for improving knowledge and enhancing therapeutic approaches.

This case is a stepping stone towards more effective, personalized care for thymic malignancies. It reminds us of the complexity of cancer care and the ongoing need for evidence-based approaches to improving patient outcomes and quality of life.

## **DATA AVAILABILITY STATEMENTS**

The authors can not publicly share the data to protect ethical considerations and participant privacy.

## **ETHICS STATEMENT**

While derived from anonymized proceedings of the monthly ONCOLLABORATE conference, this manuscript did not undergo formal ethics board review. However, the authors ensured the privacy of the case study participants was fully protected.

## **AUTHORS CONTRIBUTION**

KAT, original draft, writing of the manuscript; SLB, review and editing

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## **CONFLICT OF INTEREST**

The authors declare no conflicts of interest related to commercial or financial relationships.

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In the preparation of this manuscript, Gemini 1.5 Flash and Grammarly were utilized to refine grammatical structure and phrasing. The authors have thoroughly reviewed, edited, and verified all content generated by AI, taking full responsibility for the accuracy, integrity, and originality of the final published work. The use of AI did not extend to data analysis, interpretation of results, or the drawing of scientific conclusions. All scientific content, intellectual contributions, and research findings presented herein are solely those of the authors.

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