Complete pathologic response after concomitant pembrolizumab and radiotherapy in a patient with pretreated metastatic thymic carcinoma: a case report

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Background: Thymic carcinoma (TC) is a rare and aggressive malignancy, accounting for approximately 6% of thymic neoplasms. Due to its frequent late-stage diagnosis and poor prognosis, standard treatment typically involves multimodal therapy, including platinum-based chemotherapy, radiotherapy, and surgery. However, effective treatment options remain limited, with response rates being unsatisfactory. Recent studies have highlighted the potential of immune checkpoint inhibitors (ICIs) in treating thymic epithelial tumors, particularly in tumors with high programmed cell death ligand 1 (PD-L1) expression. Despite this, the role of ICIs in TC is still under investigation, and further research is needed to assess their efficacy and safety in clinical practice.

Case Description: We present the case of a 31-year-old male diagnosed with stage IVA squamous TC. Following disease progression after first-line chemotherapy with paclitaxel, carboplatin, and ramucirumab as part of the RELEVENT phase II trial, PD-L1 assessment revealed an 85% expression, leading to the initiation of off-label pembrolizumab (200 mg every 3 weeks). The patient subsequently developed oligoprogression with local sternal infiltration, prompting the addition of radiotherapy (10×3 Gy) alongside continued pembrolizumab. Over the following months, imaging demonstrated progressive response to treatment, culminating in a near-complete metabolic response. A residual mediastinal lesion was later surgically resected, revealing no viable tumor cells, indicative of a complete pathological response. Nine months after surgery, the patient is disease-free, with no reported immune-related adverse events.

Conclusions: This case highlights the potential of immune checkpoint inhibition combined with radiotherapy and surgery in the management of advanced TC. The patient's complete pathologic remission underscores the importance of a multidisciplinary approach. Further studies are warranted to establish ICIs as a standard treatment and optimize patient selection while mitigating immune-related toxicities.

Keywords: Thymic carcinoma (TC); immunotherapy; salvage surgery; pathologic response; case report

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Received: 15 March 2025; Accepted: 16 June 2025; Published online: 25 June 2025.
doi: 10.21037/med-25-16
View this article at: https://dx.doi.org/10.21037/med-25-16

Introduction

Background

Thymic carcinoma (TC) is a rare and aggressive malignancy arising from the thymic epithelium, accounting for 6% of all thymic neoplasms (1). Its incidence has been reported to range from 0.01 to 0.07/100,000 cases per year (2). The squamous cell subtype is the most frequent one, accounting for more than 2/3 of cases (3). Due to its aggressiveness and frequent presentation at an advanced stage, TC presents poor prognosis, with 5-year overall survival below 30% in case of stage IVA (4). Standard treatment is based on multimodal approaches, including chemotherapy, radiation therapy, and surgical resection. Despite aggressive treatment, recurrence and disease progression are common. In case of stage IVA disease, platinum-based chemotherapy is the first-line gold-standard treatment, though with unsatisfactory response rates (5). After disease progression on platinum-based therapy, second-line treatment options are traditionally limited to anthracyclines, sunitinib or everolimus (6).

Due to the rarity of TC and the lack of standardized treatment guidelines, identifying more effective therapeutic strategies remains a critical priority. In recent years, immune checkpoint inhibitors (ICIs) have shown significant antitumor activity across various malignancies, including thymic tumors.

Highlight box

Key findings
- Complete pathological response may be gained in thymic carcinoma (TC) after multidisciplinary management based on immune checkpoint inhibitors and radiotherapy.

What is known and what is new?
- Efficacy of immunotherapy in TC is still under investigation.
- Immune checkpoint inhibitors may allow for higher rate of complete pathological response within a multidisciplinary management.

What is the implication, and what should change now?
- Immunotherapy should be considered as an additional available tool in the management of advanced stage TC.

Rationale and knowledge gap

While surgical excision remains a key component of curative treatment, even in advanced stages, the role and efficacy of immunotherapy in the management of TC is still being explored. There is a need to evaluate the feasibility and outcomes of such multidisciplinary approaches.

Objective

Herein, this case report describes the successful multidisciplinary management of a stage IVA squamous TC using ICI, radiotherapy and surgical excision in a pretreated patient. This case report is written following the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-25-16/rc).

Case presentation

A 31-year-old male presented to the emergency department with exertional dyspnea, cough, chest pain, and weight loss. Whole body contrast-enhanced computed tomography (CT) scan and fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a large mass of 9 cm × 10 cm × 11 cm, with glucose uptake (standardized uptake value maximum 17), within the anterior mediastinal compartment, together with enlarged paratracheal and supraclavicular lymph nodes and subpleural nodules (*Figure 1*). Supraclavicular node excisional biopsy according to Daniels was performed and the histological examination revealed a TC with squamous differentiation (*Figure 2*), classified as stage IVA (T3N1M1a) according to 9th tumor-node-metastasis (TNM) edition (7).

The patient was enrolled in the RELEVENT phase II trial (8), receiving paclitaxel (200 mg/m^2 IV, day 1, every 21 days, for 6 cycles), carboplatin [area under the curve (AUC) =5, day 1, every 21 days, for 6 cycles], and ramucirumab (10 mg/kg, day 1, every 21 days, for 6 cycles). After six cycles, partial remission was achieved, without any observed toxicity, and the patient continued on Ramucirumab maintenance therapy (10 mg/kg every 3 weeks). Nonetheless, 8 months later, radiologic progression was confirmed, leading to the conclusion of the RELEVENT trial.

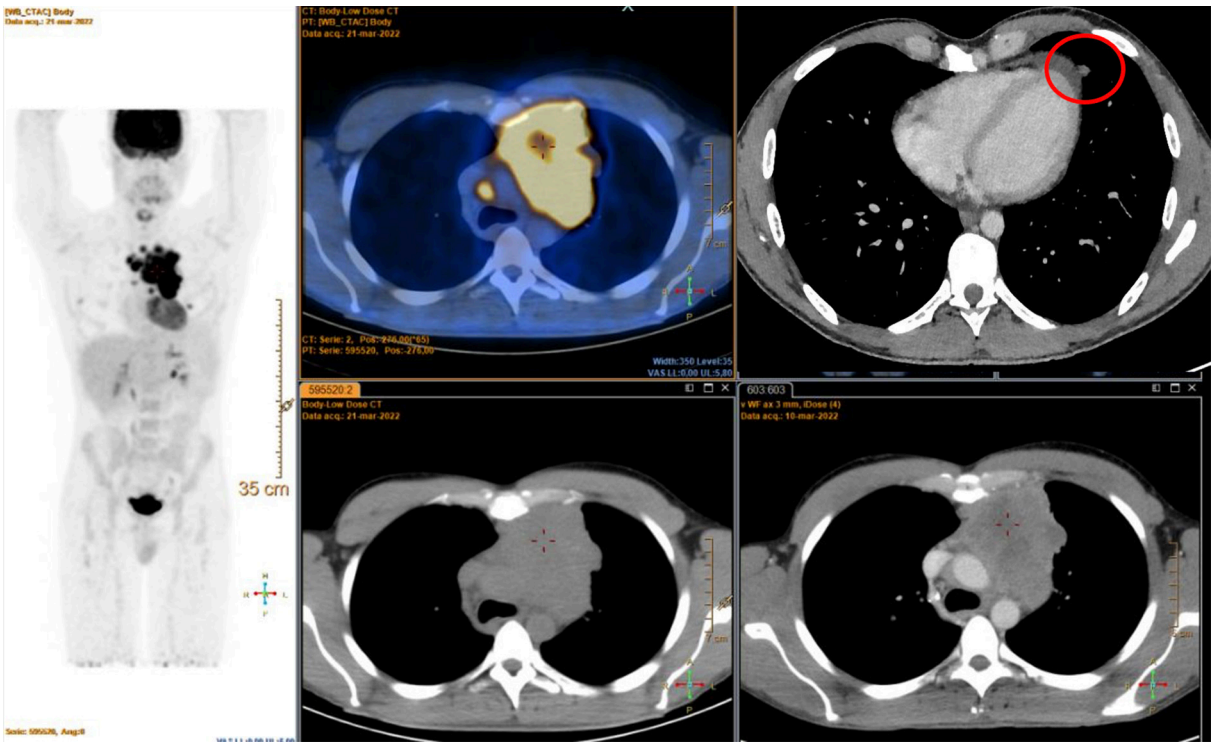

Figure 1 FDG-PET and chest CT scan showing the onset of the disease. Red circle highlights one of the pleural nodules. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

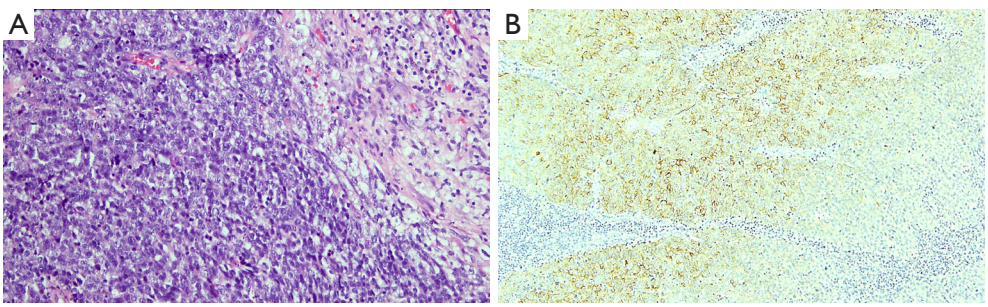

Figure 2 Histologic examination showing poorly differentiated neoplasm (A; H&E staining, 200×) with epithelial differentiation (B; pan-cytokeratins 200×; IHC staining), and variable expression of p40, CD5 and PAX8 (not shown), consistent with squamous cell carcinoma of thymic origin. H&E, hematoxylin and eosin; IHC, immunohistochemistry.

Programmed cell death ligand 1 (PD-L1) immunohistochemical assessment of the tumor tissue revealed 85% expression, leading to an off-label administration of pembrolizumab (200 mg every 3 weeks). Three months later, CT imaging indicated oligoprogression with local sternal infiltration, causing increased chest pain. The patient initiated local radiotherapy (10×3 Gy) (*Figure 3*) together with denosumab (120 mg subcutaneously), with significant pain decrease and no adverse events, while continuing pembrolizumab for one year.

Three months after radiotherapy, the CT scan demonstrated partial remission; 9 months later, further treatment response was noted. Twelve months later, FDG-PET/CT scan revealed a near-complete metabolic response (*Figure 4*).

CT scan showed stable near-complete resolution, except

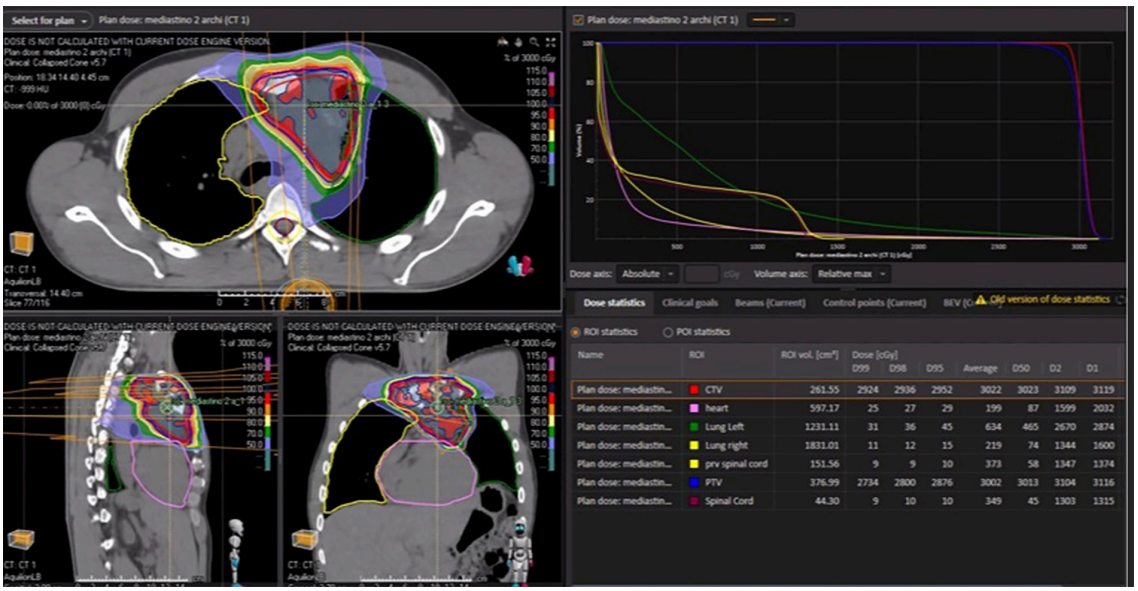

Figure 3 Radiotherapy treatment plan for upper mediastinum. The dose distribution is displayed in axial, sagittal, and coronal views, highlighting the targeted region and surrounding structures. The treatment consists of 10 fractions of 3 Gy (total dose: 30 Gy) delivered with VMAT using a 6 MV photon beam. The target volume includes the involved site in the upper mediastinum, with daily CBCT for IGRT to ensure precise positioning and dose delivery. The isodose lines indicate different dose levels, optimizing tumor coverage while sparing surrounding organs at risk. CBCT, cone beam computed tomography; IGRT, image-guided radiation therapy; MV, megavoltage; VMAT, volumetric-modulated arc therapy.

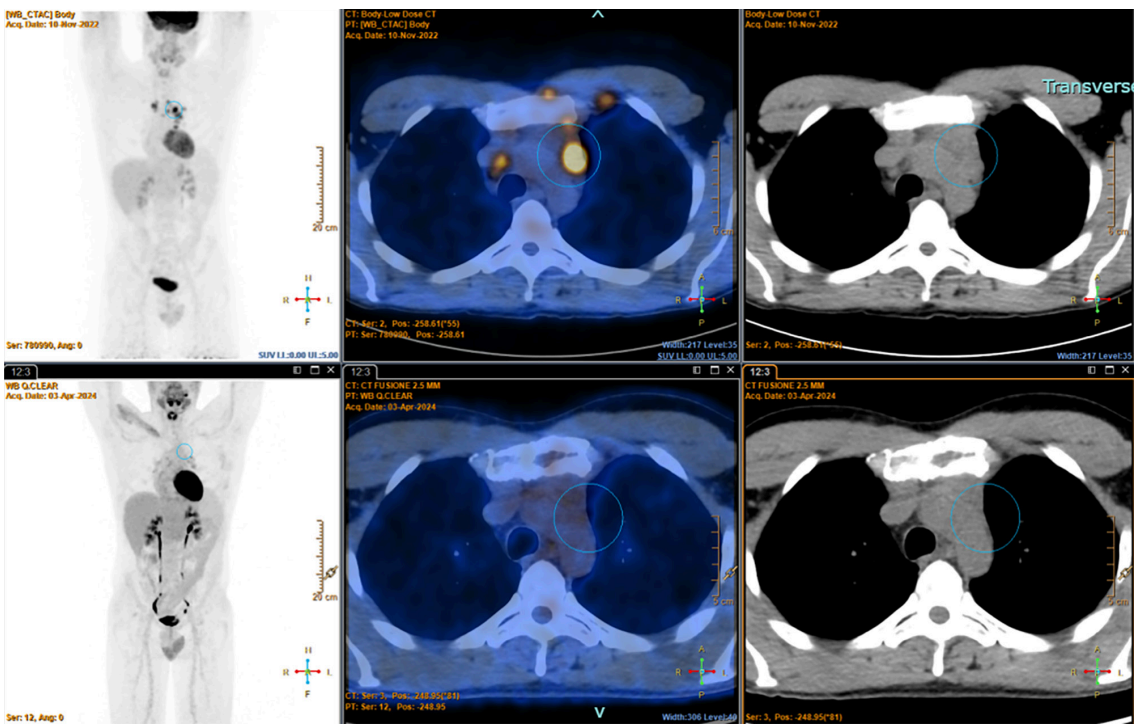

Figure 4 FDG-PET/CT scan showing the significant response of disease to the treatment. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography.

for a residual lesion in the anterior mediastinum, later confirmed by chest MRI (*Figure 5*).

Given the patient's clinical stability and treatment response, after shared multidisciplinary discussion, surgical resection was recommended. The patient underwent a left-sided video-assisted thoracoscopic surgery biportal resection of the residual mediastinal lesion *en-bloc* with portion of the left upper lung lobe, together with random pleural biopsies. The surgical field exhibited extensive and dense fibrosis, predominantly on the sternal side. Nonetheless, the sternal margin of the excised lesion was evaluated by frozen section analysis and was free of tumor, leading to preservation of the sternum.

Histopathologic assessment detected, both macro- and microscopically, a thick, fibrotic, cavitated nodule centered by necrosis with calcifications and cell shadows, with foci of reactivity for broad spectrum cytokeratins, attached to the mediastinal pleura (*Figure 6*), consistent with a complete response to prior therapy.

The postoperative course was uneventful, the chest drain was removed three days later, and the patient was discharged on 5th postoperative day.

Nine months after surgery, the patient is alive without evidence of disease (*Figure 7*). No immune-related adverse events (irAEs) were recorded.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

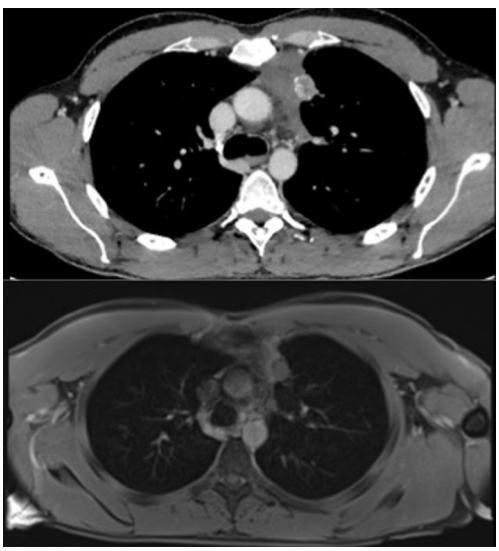

Figure 5 Chest CT and chest MRI scans showing the residual thymic nodule. CT, computed tomography; MRI, magnetic resonance imaging.

Discussion

PD-L1 is widely expressed in several solid tumors and serves as a key biomarker for predicting response to ICIs (9). Studies have demonstrated that both malignant thymomas and TCs frequently exhibit high PD-L1 expression, suggesting that immunotherapy could be a viable treatment approach (10). However, the use of programmed cell death protein 1 (PD-1) inhibitors in thymic tumors requires caution due to the potential for irAEs, particularly in patients with thymomas, which are often linked to autoimmune disorders. B-type thymomas contain lymphocytes as part of their tumor composition, increasing the risk of excessive immune activation and severe autoimmune complications (11). In contrast, thymic

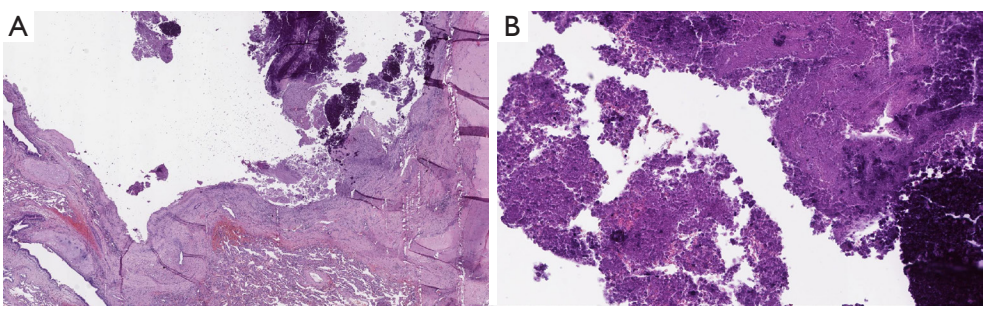

Figure 6 Post-therapy assessment shows a cavitated lesion attached to the visceral pleura (A; H&E staining, 20×), composed of fibrotic and necrotic tissue, with cell shadows and calcifications (B; H&E staining, 400×). H&E, hematoxylin and eosin.

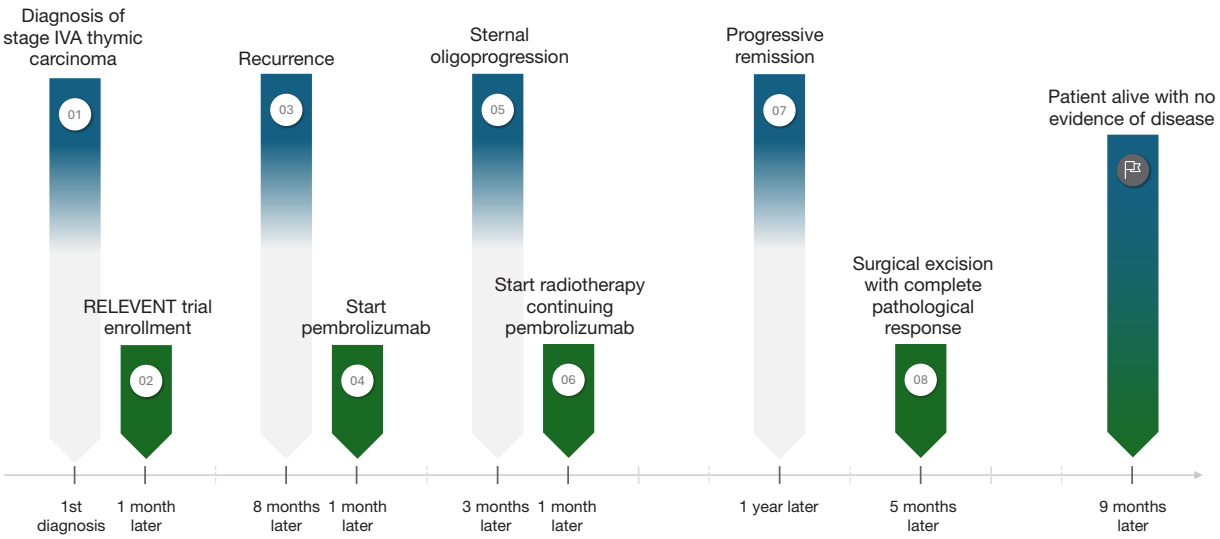

Figure 7 Case report timeline.

squamous carcinoma lacks a significant lymphocytic component, resulting in a much lower incidence of irAEs (12).

Multiple studies have explored the potential of ICIs in the treatment of thymic epithelial tumors (TETs) (13). Thymic tumoral epithelial cells exhibit higher PD-L1 expression than normal thymic tissue, with an inverse correlation between expression levels and clinical outcomes. These findings suggest that targeting the PD-1/PD-L1 pathway with monoclonal antibodies could offer a promising therapeutic strategy for TCs.

The efficacy of pembrolizumab, an anti-PD-L1 agent, was assessed in a phase II, single-arm, single-center trial involving 40 patients with recurrent TC who had progressed after at least one line of chemotherapy (14). The study reported an objective response rate of 22.5%, including one complete response, whereas 53% of patients achieved stable disease. The median progression-free survival (PFS) was 4.2 months, with significantly longer PFS observed in patients with high PD-L1 expression (tumor proportion score ≥50%) compared to those with low or absent expression (24 *vs.* 2.9 months).

Another phase II trial evaluated pembrolizumab in 33 patients with TET who had previously failed platinum-based chemotherapy (15). The study demonstrated a response rate in TC of 19%, and a median PFS of 6.1 months, reaffirming the predictive value of high PD-L1 expression in treatment response. On the other hand, less favorable outcomes were reported in a phase II study of nivolumab in 15 previously treated TC patients, with no objective responses (16).

Radiotherapy plays a critical role in the multimodal treatment of TC. Its primary applications include postoperative adjuvant therapy to reduce the risk of local recurrence, particularly in patients with positive surgical margins or advanced-stage disease; definitive treatment for unresectable tumors, typically combined with chemotherapy to achieve local control and symptom relief; and palliative radiotherapy for symptom management, such as alleviation of pain or relief from airway compression in metastatic settings (17,18). Advanced radiotherapy modalities, such as intensity-modulated radiation therapy (IMRT) and proton therapy, are recommended to minimize radiation exposure to adjacent critical mediastinal structures, including the heart, lungs, and spinal cord (19). Recent evidence indicates that radiotherapy provides effective local tumor control with minimal toxicity even in patients with metastatic thymic malignancies (20,21).

Radiotherapy in combination with pembrolizumab has shown potential therapeutic synergy across multiple malignancies, including TC, by enhancing anti-tumor immune responses. Radiotherapy may promote immunogenic cell death and upregulate PD-L1 expression, thereby potentially augmenting the efficacy of immune checkpoint blockade. Clinical evidence suggests improved outcomes with this combination, particularly in locally advanced or treatment-refractory cases (22).

However, a concerning point is the incidence of irAEs; indeed, previous studies have shown a higher incidence of irAEs in patients with thymic tumors, particularly

myasthenia gravis, lethal myocarditis, and other severe reactions (23). The presence of immature T lymphocytes is a key factor in the development of autoimmunity in thymic malignancies (24). Nonetheless, patients with thymic squamous carcinoma, which lacks immature immune cells, have a lower risk of developing autoimmunity after PD-1 inhibitor treatment (14,15).

Notably, our patient did not develop any irAEs.

Collectively, literature highlighted the promising role of ICIs targeting the PD-1/PD-L1 axis in advanced TC, so that the National Comprehensive Cancer Network (NCCN) has recognized pembrolizumab as a viable second-line treatment option, particularly in patients with high PD-L1 expression, underscoring the growing relevance of immunotherapy in this challenging malignancy (25).

This report presents the unique case of a young patient diagnosed with stage IV squamous TC, in progression during first-line chemotherapy, treated with off-label pembrolizumab, later presenting a sternal oligo-progression treated with radiation therapy and finally undergoing minimally invasive surgical excision of the residual mediastinal lesion, revealing a complete pathological response.

On the other hand, this case has some limitations: the follow-up is short, and it is still ongoing, therefore long-term outcomes are still to be investigated; PD-L1 overexpression has still uncertain meaning in TETs; comprehensive genetic analysis was not conducted; therefore, additional potential target mutations may have gone undetected; metabolic uptake to the sternum was not biopsied and pseudo-progression has not been definitely ruled out. It is possible that the entire mass increased in size, but only the anterior portion produced symptoms due to the limited expansibility of the surrounding anatomical compartment. Additionally, pembrolizumab therapy was continued during radiotherapy, which may explain why the mass did not regress prior to radiotherapy, as immunotherapy was still ongoing. Importantly, neither PET nor CT imaging identified any additional suspicious lesions, and histological examination of the surgical specimen revealed no residual tumor cells, even outside the irradiated area, as confirmed by random pleural biopsies. Therefore, although the exact mechanism remains uncertain, the combination of radiotherapy and pembrolizumab appears to have been effective in achieving local disease control.

Furthermore, it may be questioned why surgical resection was pursued despite the apparent effectiveness of pembrolizumab. Pembrolizumab induced an excellent near-complete metabolic and radiologic response; however, concern remained that the residual mediastinal lesion could serve as a reservoir for mutated tumor cells, potentially leading to further disease progression. Therefore, surgical excision was performed.

The patient was very satisfied with the multidisciplinary tailored multicenter approach adopted for him.

Conclusions

TC remains a challenging malignancy with limited effective treatment options. This case highlights the potential efficacy of ICIs, particularly in high PD-L1 expressors, when combined with radiotherapy and surgery. The patient's complete pathologic remission underscores the importance of a multidisciplinary approach. Further studies are needed to establish ICIs as a standard treatment and better predict responders while mitigating immune-related toxicities.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Malgorzata Szolkowska) for "The Series Dedicated to the 14th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2024)" published in *Mediastinum*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-25-16/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-25-16/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-25-16/coif). "The Series Dedicated to the 14th International Thymic Malignancy Interest Group Annual Meeting (ITMIG 2024)" was commissioned by the editorial office without

any funding or sponsorship. P.M. serves as an unpaid editorial board member of *Mediastinum* from January 2025 to December 2026. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/med-25-16
Cite this article as: Mendogni P, Orlandi R, Spizzo G, Damiani D, Maffei M, Croci GA, Tosi D. Complete pathologic response after concomitant pembrolizumab and radiotherapy in a patient with pretreated metastatic thymic carcinoma: a case report. Mediastinum 2025;9:21.

