Case Report: iMDT Corner

Stage III–IV thymic squamous cell carcinoma in complete pathological remission achieved with thymic cancer resection after immunotherapy combined with chemotherapeutic conversion therapy: a report of two cases from real-world data

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Background: Thymic carcinoma, a rare malignancy in the mediastinum, currently lacks standardized treatment options. Although surgery remains a crucial component among traditional therapeutic approaches, the potential benefits of radiotherapy and chemotherapy remain controversial. Nevertheless, a substantial number of patients are diagnosed with advanced tumor growth, posing challenges for achieving complete resection through surgical intervention and resulting in a poor prognosis. In light of the promising antitumor effects demonstrated by immunotherapy in various prevalent cancers, certain studies have shown favorable efficacy in advanced or recurrent thymic cancer cases. However, the incidence of adverse effects induced by immunotherapy in thymic cancer is notably higher compared to other tumor types, with severe and fatal complications being particularly significant. Consequently, there is an urgent need to address the crucial issue of patient selection for immunotherapy in thymic cancer.

Case Description: In this study, we report on the treatment with programmed cell death protein 1 (PD-1) inhibitor therapy combined with chemotherapy conversion therapy for two patients diagnosed with stage III–IV thymic squamous cell carcinoma according to the Masaoka-Koga staging system. The aim of this study was to assess the effectiveness and safety of PD-1 inhibitor combined with chemotherapy conversion therapy in patients with thymic squamous cell carcinoma. Two patients in this cohort, one with stage III and another with stage IV disease, were deemed ineligible for upfront surgical resection. Puncture pathology confirmed the diagnosis of thymic squamous cell carcinoma. Both patients underwent transformation therapy using a combination of PD-1 inhibitors and chemotherapy. Tumor shrinkage was observed in both patients, enabling successful completion of surgery. Postoperative pathology revealed no residual tumor cells, indicating complete pathological remission. Notably, none of the patients experienced grade 3 or higher immunotherapy-related adverse reactions following immunotherapy.

Conclusions: A combination of PD-1 inhibitors and chemotherapy followed by surgery demonstrated improved efficacy and enhanced safety for treating patients with Masaoka-Koga stage III–IV thymic squamous carcinoma and represents a potential novel therapeutic alternative for this disease.

Keywords: Thymic squamous carcinoma; programmed cell death protein 1 inhibitor (PD-1 inhibitor); complete pathological remission; case report

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Introduction

Thymoma is an uncommon neoplasm arising from the thymus epithelium, with a prevalence of 0.2–1.5% among malignant tumors (1). Based on the relative proportion of epithelial cells to lymphocytes in thymic tumors, thymomas are classified by the World Health Organization (WHO) into low grade thymomas (types A and AB), high-grade thymomas (types B1, B2 and B3) and thymic carcinomas (type C) (2). In the past, malignant thymoma and thymic carcinoma were managed in a similar manner, with surgical resection being advocated as the primary treatment modality (3-5). However, a considerable number of patients presents with tumor infiltration into vital structures, such as the pericardium, innominate vein, and superior vena cava, rendering complete resection through direct surgery challenging. Furthermore, the efficacy of postoperative radiotherapy and chemotherapy in thymic carcinoma has been found to be unsatisfactory. Although a phase II clinical study in Japan indicated the efficacy of lenvatinib for unresectable thymic carcinoma patients, the objective response rate was only 38% (6). Hence, the prognosis of patients suffering from diseases in an advanced stage is unfavorable (7). Given the low incidence and absence of standardized treatment protocols for thymic carcinoma, the search for a more efficacious approach to enhance patient prognoses is of utmost importance. In recent years, immune checkpoint inhibitors (ICIs) have demonstrated notable antitumor effects in the treatment of various types of cancer, including thymic tumors.

High expression of programmed cell death ligand 1 (PD-L1) in various solid tumors serves as an effective biomarker for the use of ICIs in patients. It has been observed that malignant thymoma and thymic carcinoma cells exhibit a high level of PD-L1 expression, suggesting that immunotherapy could be a promising treatment option for thymic tumors (8,9). However, it should be noted that thymomas are often associated with autoimmune diseases, and the administration of programmed cell death protein 1 (PD-1) inhibitors may potentially lead to significant immune-related adverse events (irAEs) as a result of autoimmune system activation (10,11). B-type thymomas, irrespective of their risk profile, present lymphocytes as a constituent of the pathological component. This subset of lymphocytes may undergo excessive activation, thereby inducing autoimmune damage and even life-threatening adverse events. In contrast, thymic squamous carcinoma exhibits a squamous epithelial pathology and lacks lymphocytes. Consequently, the incidence of irAEs is considerably lower compared to that of thymoma. Previous investigations have indicated there to be a substantial disparity between malignant thymoma and thymic squamous carcinoma concerning the efficacy and adverse events associated with immunotherapy, particularly severe irAEs (7,12,13). Consequently, the differential treatment of thymoma and thymic carcinoma, particularly in the selection of therapeutic regimens such as ICI therapy, is warranted. We present this article in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-488/rc).

Highlight box

Key findings

- Thymic squamous cell carcinoma can be efficaciously and safely treated with programmed cell death protein 1 (PD-1) inhibitors.

What is known and what is new?

- It has been established that PD-1 inhibitors offer a potential treatment option for thymic malignancies.
- This is the first report of 2 cases in which thymic carcinoma immunization combined with chemotherapy followed by surgery resulted in complete pathological remission with a low rate of adverse reactions. However, it is crucial to differentiate between type B and type C thymoma. Immunotherapy for type B thymoma is associated with a higher risk of severe adverse reactions and should be avoided whenever feasible. Conversely, type C thymic carcinoma, often squamous carcinoma subtype, shows promising response to immunotherapy.

What is the implication, and what should change now?

- The combination of PD-1 inhibitors and chemotherapy followed by surgery for patients with thymic squamous cell carcinoma demonstrates improved efficacy and safety, thus offering a potential new treatment option for stage III–IV thymic squamous carcinoma.

Case presentation

All procedures performed in this study were in accordance

Table 1 Clinical features of patients diagnosed with thymic carcinoma

Case	Age (years)	Pectoralgia	Myasthenia	Masaoka-Koga stage	Treatment	Follow-up time	Current condition
1	39	Yes	Never	III	PD-1 inhibitor, chemotherapy and surgery	12 months	Without recurrence
2	52	Never	Never	IV	PD-1 inhibitor, chemotherapy and surgery	12 months	Without recurrence

PD-1, programmed cell death protein 1.

Table 2 Radiographic features of thymic carcinoma

Case	Size (imageology)		Vessels invaded	Pleural effusion	Metastasis
	Before	After			
1	72 mm × 67 mm	44 mm × 36 mm	Ascending aorta, pulmonary artery, left innominate vein	Never	Liver
2	57 mm × 58 mm	11 mm × 28 mm	Left subclavian artery, aorta, left brachiocephalic vein	Never	Never

with the ethical standards of the Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University and with the Helsinki Declaration (revised in 2013). Written informed consents were obtained from the patients for publication of this case report and accompanying images. Copies of the written consents are available for review by the editorial board of this journal.

Case 1

A 39-year-old male patient was admitted to The Third Affiliated Hospital of Chongqing Medical University with a 1-year history of left-sided intermittent chest pain, which worsened over the course of 2 months. The patient showed no ocular or limb weakness, dysphagia, or dyspnea, and denied any family history of thymic tumor (*Table 1*). A chest computed tomography (CT) scan revealed a left anterior superior mediastinal tumor measuring 72 mm × 67 mm in size, characterized by uneven density and significant enhancement. The tumor exhibited a close association with the ascending aorta and pulmonary artery, as well as a filling defect in the left cephalic and brachial veins. The presence of liver metastasis was also detected. The classification is stage IV according to the Masaoka-Koga staging system that precluded direct surgical intervention. CT-guided puncture biopsy pathology confirmed the diagnosis of low-differentiated squamous carcinoma with a PD-L1 tumor proportion score (TPS) of 75%. Following treatment with a combination of PD-1 checkpoint inhibitors (sintilimab 200 mg) albumin-bound paclitaxel (240 mg/m^2) and carboplatin [area under the curve (AUC) =5] over a period of 4 cycles, subsequent CT examination demonstrated tumor regression to a size of 44 mm × 36 mm. Furthermore, the relationship between the tumor and the ascending aorta, pulmonary artery, and the left cephalic and brachial veins was more clearly defined compared to previous observations (*Table 2*). In accordance with the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines, the therapeutic outcome has been classified as Partial Response (14). Positron emission tomography (PET)-CT assessment confirmed the active status of the tumor, with no discernible metastases aside from the liver lesion. Following extensive interdisciplinary deliberation, the patient underwent tumor regression treatment, with a complete excision procedure anticipated. Subsequent to obtaining informed consent, a central sternotomy was performed. Throughout the surgical procedure, it was observed that the tumor exhibited close proximity to the pulmonary artery and the aorta, yet it remained amenable to separation. Additionally, the tumor was found to have infiltrated the pericardium encompassing the excision of the mediastinal tumor and partial pericardial resection. Postoperative histopathology revealed fibrous tissue hyperplasia within the mediastinal tissue accompanied by the presence of cholesterol crystals and significant infiltration of inflammatory cells. Locally, a substantial presence of foam cells was observed, while malignant cells were conspicuously absent. Consequently, the patient achieved a comprehensive

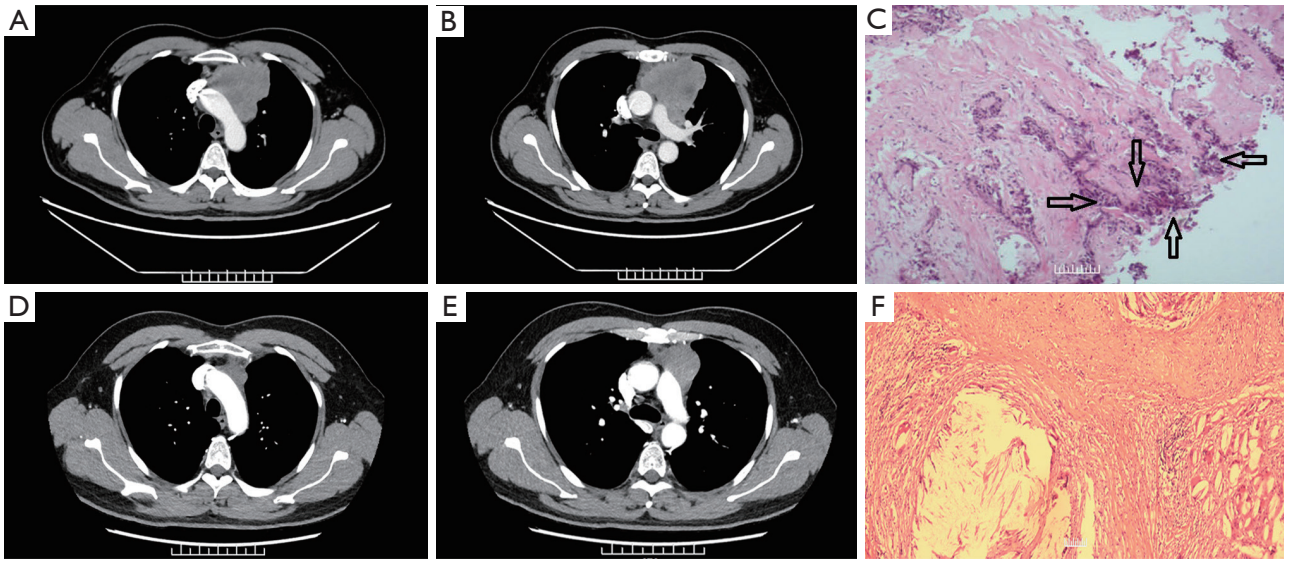

Figure 1 Imaging findings and pathological results of case 1. (A,B) Imaging features of contrast-enhanced CT before treatment; (C) pathological results before treatment (tumor cells indicated by arrows): the pathological findings indicate that the tumor located in the anterior mediastinum is a squamous cell carcinoma with a low degree of differentiation [CK (+++), P40 (+++), P63 (+++), NAPSIN A (–), CD56 (–), TTF-1 (–), SYN (–), Ki-67 70%] (HE, ×40); (D,E) imaging features of contrast-enhanced CT after treatment; (F) pathological results after surgery (HE, ×100). CT, computed tomography; HE, hematoxylin and eosin.

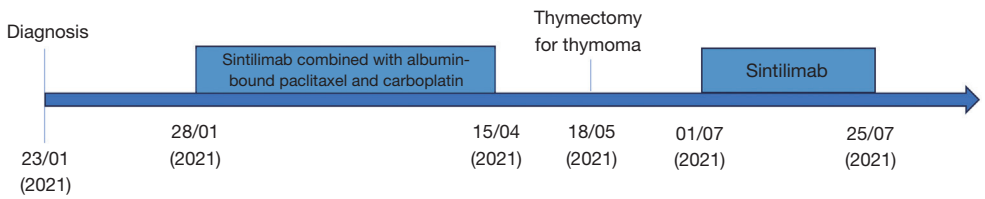

Figure 2 The timeline for all treatments of case 1.

pathological remission (*Figure 1*). The patient underwent two cycles of sintilimab as adjuvant therapy following the surgical procedure. Subsequent follow-up evaluations at 3, 6, and 12 months post-surgery, using enhanced CT scans of the chest, showed no evidence of tumor recurrence or metastasis (*Figure 2*). The patient experienced a number of adverse reactions subsequent to medication, including alopecia, nausea, and arthralgia, which were plausibly associated with the administration of chemotherapeutic agents. Furthermore, transient immune-mediated hepatitis developed subsequent to the initial drug cycle, primarily manifesting as elevated levels of bilirubin (indirect bilirubin: 12.0 μmol/L, ref. value 1.7–10.2 μmol/L). In accordance with guidelines for managing irAEs associated with ICIs, this adverse reaction was classified as grade I (15). The patient experienced complete recovery upon receiving hepatoprotective treatment, displaying no recurrence during subsequent therapeutic intervention. Furthermore, a transient case of immune-related myocardial injury was observed, manifesting as a mild elevation in cardiac troponin I levels (cardiac troponin I 0.187 ng/mL, ref. value 0–0.03 ng/mL), with electrocardiographic findings remaining unremarkable. Following treatment, the patient's cardiac troponin I levels returned to normal and did not exhibit subsequent elevation, negating any impact of the use of PD-1 inhibitors. Additionally, transient hyperthyroidism was evident in the form of a slight elevation in serum T4 levels (total thyroxine T4 156.78 nmol/L, ref. value 73.74–137.15 nmol/L), which spontaneously resolved without therapeutic intervention (*Table 3*).

Table 3 Immune-related adverse events of thymic carcinoma

Adverse events	Case 1			Case 2		
	Any grade	Grade 3–5	Time	Any grade	Grade 3–5	Time
Alopecia	√	×	3 weeks	√	×	2 weeks
Neutropenia	×	×		×	×	
Nausea	√	×	1 week	√	×	1 week
Diarrhea	×	×		×	×	
Arthralgia	√	×	1 week	√	×	1 week
Rash	×	×		×	×	
Pneumonitis	×	×		×	×	
Hepatitis	√	×	3 weeks	√	×	3 weeks
Colitis	×	×		×	×	
Thyroiditis	√	×	3 weeks	×	×	
Neuropathies	×	×		×	×	
Nephritis	×	×		×	×	
Anemia	×	×		×	×	
Myocarditis	√	×	12 weeks	×	×	

Case 2

A 52-year-old female patient was admitted to The Third Affiliated Hospital of Chongqing Medical University with a mediastinal tumor that had been detected on a CT scan 6 days prior. She did not exhibit any ocular or generalized muscle weakness and had no familial history of thymic tumors (*Table 1*). The chest CT scan revealed a left anterior superior mediastinal tumor 57 mm × 58 mm in size with slight enhancement that was infiltrating the pericardium, left subclavian artery, left innominate vein, and thoracic aorta. The classification is stage III according to the Masaoka-Koga staging system, indicating that direct surgical resection of the mediastinal tumor was not feasible. Puncture biopsy pathology identified the tumor as low-grade squamous carcinoma with a PD-L1 TPS of 85%. Following 4 cycles of Albumin-bound paclitaxel (240 mg/m^2) combined with carboplatin (AUC =5) with sintilimab (200 mg), a CT scan demonstrated tumor reduction to a size of 11 mm × 28 mm, with improved demarcation from the peripheral arteries and pericardium (*Table 2*). In accordance with the RECIST version 1.1 guidelines, the therapeutic outcome has been classified as partial response. After a multidisciplinary discussion, the treatment plan devised involved achieving tumor shrinkage with the intention of complete resection. The patient consented and subsequently underwent a median sternotomy for mediastinal tumor resection partial pericardiectomy, and partial removal of the left innominate vein, because it was found that the tumor invaded the left innominate vein and the pericardium. Postoperative pathological analysis revealed chronic inflammatory cell infiltration with necrosis in the mediastinal tumor tissue, displaying complete pathological remission (*Figure 3*). The patient underwent two cycles of sintilimab as adjuvant therapy following the surgical procedure (*Figure 4*). During the 3-, 6-, and 12-month postoperative follow-ups, enhanced CT scan of the chest showed no tumor recurrence or metastasis. The patient experienced chemotherapy-related adverse reactions, including alopecia, nausea, and arthralgia. Additionally, the patient encountered transient immune-related hepatitis after the first cycle, primarily manifesting as a mild elevation in Alanine transaminase levels (ref. value 7.0–40.0 U/L). However, with appropriate hepatoprotective treatment, liver function returned to normal and subsequent treatment, including the use of PD-1 inhibitors, was unaffected (*Table 3*).

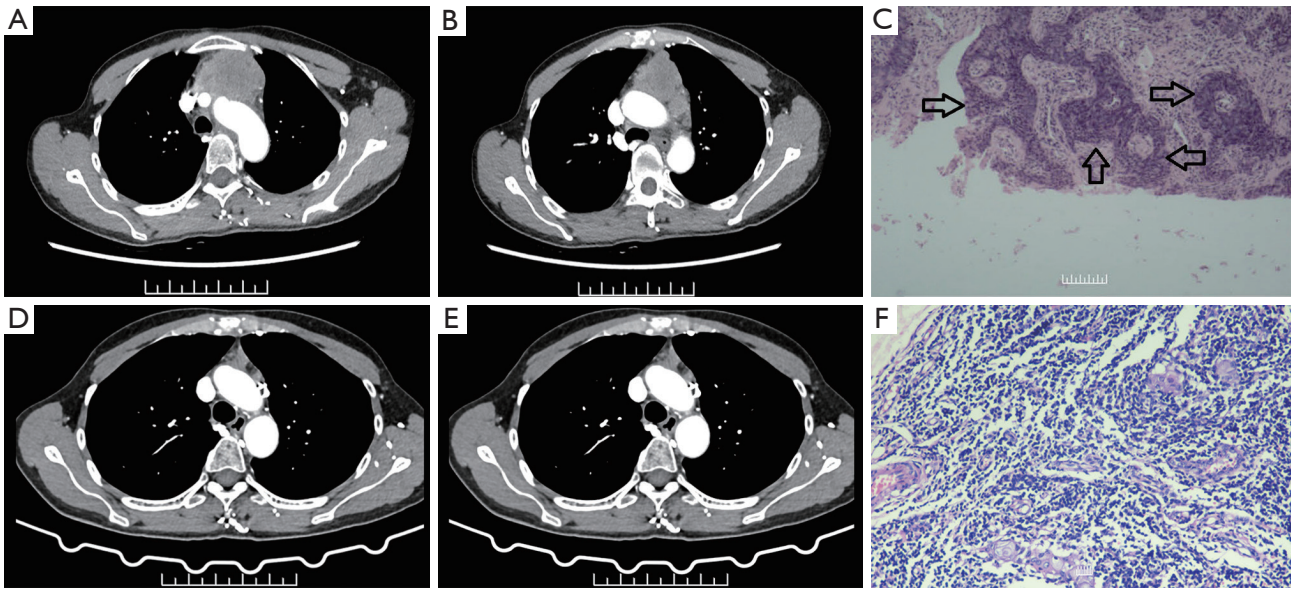

Figure 3 Imaging findings and pathological results of case 2. (A,B) Imaging features of contrast-enhanced CT before treatment; (C) pathological results before treatment (tumor cells indicated by arrows): the pathological findings indicate that the tumor located in the anterior mediastinum is a squamous cell carcinoma with a low degree of differentiation [CK (+++), P40 (+), P63 (+++), CD99 (+++), TDT (–), CD56 (–), TTF-1 (–), Ki-67 40%] (HE, ×40); (D,E) imaging features of contrast-enhanced CT after treatment; (F) pathological results after surgery (HE, ×100). CT, computed tomography; HE, hematoxylin and eosin.

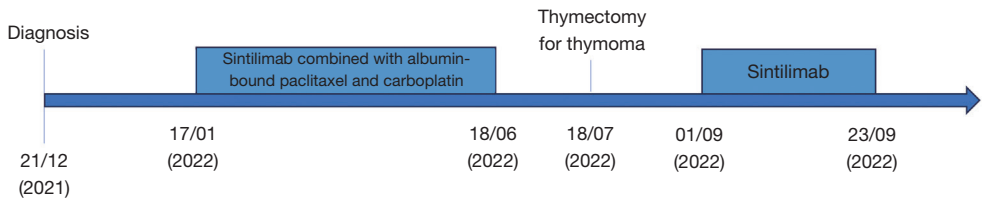

Figure 4 The timeline for all treatments of case 2.

International multidisciplinary team (iMDT) discussion

Thymoma and thymic carcinoma

Thymic carcinoma and high-grade thymoma are both neoplasms originating from the thymic epithelium, but they display distinct clinical, pathological, and histological characteristics (16). Thymic carcinoma is an infrequent malignancy originating from the thymus, with a significantly lower incidence than thymoma. A study has reported that thymic carcinoma accounts for approximately 10% to 15% of all thymomas (17). Clinical presentation of thymic carcinoma closely resembles that of malignant thymoma, with symptoms including chest pain, back pain, chest tightness, and signs of tumor compression such as superior vena cava obstruction. However, thymic carcinoma is less commonly associated with myasthenia gravis compared to thymoma (18,19). Radiographic findings indicate that thymic carcinoma is more likely to invade larger blood vessels and the pericardium, leading to pericardial effusion and lymph node enlargement (20). Within our study cohort, neither patient had a notable family history of tumors or myasthenia gravis. The occurrence of chest pain was reported in one patient, while incidentally, during a routine physical examination, thymic carcinoma was detected in another patient. Imaging analyses demonstrated marked enhancement and aggressive behavior of the tumor. At the time of diagnosis, the tumor had already invaded critical organs, including the pericardium, aorta, and pulmonary artery trunk. In case 1, liver metastasis was also

evident. These clinical features align with previous reports. Importantly, thymic carcinoma and thymoma exhibit distinctive pathological characteristics. Thymic squamous carcinoma represents the most prevalent histological subtype of thymic carcinoma (21). The cells of thymic squamous carcinoma resemble those of solid squamous carcinomas without lymphocyte infiltration or typical thymic tissue characteristics. The differing pathological subtypes of thymic carcinoma and thymoma contribute to variations in the efficacy of immunotherapy and the incidence of associated adverse effects.

Immunotherapy efficacy

ICIs have gained widespread use in the treatment of various solid tumors due to their notable antitumor effects. Among the myriad of potential biomarkers, the expression level of PD-L1 has emerged as a reliable and effective indicator. Thymic tumors originating from immune organs often exhibit heightened levels of PD-L1 expression. This observation provides a compelling rationale for the implementation of immunotherapy strategies in patients with thymic tumors (9,22). Pioneering work by Giaccone *et al.* involved a phase II clinical trial that investigated the efficacy of the PD-1 inhibitor pembrolizumab in recurrent thymic cancer. The results included a median follow-up time of 20 months and an objective remission rate (ORR) of 22.5% in the patient cohort. Notably, complete remission was achieved in 1 patient (3%) while 8 patients (20%) experienced partial remission. Furthermore, 21 patients (53%) exhibited stable disease, with only 27% showing progression. The average duration of remission was 22.4 months. The median progression-free survival (PFS) for the overall study population was 4.2 months, and the median overall survival (OS) was 24.9 months. Strikingly, patients with high levels of PD-L1 expression demonstrated a prolonged PFS of 25 months in stark contrast to those with low or negative PD-L1 expression (2.9 months) (23). A subsequent study was conducted in South Korea to investigate the therapeutic efficacy of pembrolizumab, an ICI, in patients with advanced, previously treated thymic tumors. The study findings revealed that only 27% of the patients experienced disease progression, which closely corroborated the results obtained from a prior study conducted in the United States (24). These collective observations substantiate the strong therapeutic potential of PD-1 inhibitors for the treatment of thymic cancer. In our study cohort, the two patients were subjected to a combination therapy involving PD-1 inhibitors and chemotherapy. Based on the RECIST evaluation criteria, they both exhibited partial relief, and complete pathological remission was confirmed by surgical pathology, a rarity in previous radiotherapy approaches. Given the compelling outcomes from earlier investigations, coupled with the remarkable therapeutic responses observed in our study, it can be inferred that the combination of immunotherapy and chemotherapy holds significant promise for effectively targeting thymic squamous carcinoma.

Safety

The efficacy of antitumor therapy in targeting thymic tumors must be considered in relation to the potential for serious adverse reactions associated with the use of PD-1 inhibitors. This heightened incidence of adverse events might be attributed to the immunological nature of the thymus as an immune organ. Previous investigations have provided evidence for an increased occurrence of irAEs among patients with thymic tumors, particularly, but not exclusively, myasthenia gravis, lethal myocarditis, and other severe reactions, when compared to other forms of cancer (25,26). The underlying mechanism primarily involves the ability of thymic neoplastic epithelium to influence the differentiation of $CD4^+$ and $CD8^+$ lymphocytes, along with the absence of functional thymic medulla in thymomas. Consequently, auto-reactive T cells elude capture within the circulatory system, thereby instigating autoimmune phenomena. The presence of immature T lymphocytes plays a crucial role in the development of autoimmunity within the context of thymic malignancies (27,28). In contrast to patients with thymoma, which lacks immature immune cells, those with thymic squamous carcinoma exhibit a lower propensity to develop autoimmunity following treatment with PD-1 inhibitors (13). For instance, a US trial reported cases of severe myositis or cardiomyositis in three patients with thymoma, severe hepatitis in 10% of cases, and a rare occurrence of myasthenia gravis in one patient, whereas such events were uncommon among individuals with squamous carcinoma of the thymus treated with PD-1 inhibitors (23). Similarly, a Korean study indicated that 15.4% of patients with thymic carcinoma experienced severe hepatic impairment, contrasting with a significantly higher incidence of 71.6% among patients with thymoma (24). A separate investigation demonstrated that the incidence of exacerbating myasthenia gravis and severe myocarditis following immunotherapy

in cases of thymoma was 5% and 57%, respectively, in comparison to squamous carcinoma of the thymus or other types of malignancy (23). This evidence establishes a substantially reduced occurrence and severity of serious irAEs in patients with thymic carcinoma as compared to those with thymoma. In our cohort, the two patients with thymic squamous carcinoma underwent treatment involving a combination of PD-1 inhibitors and chemotherapeutic conversion therapy, leading to a 100% incidence of adverse reactions. The majority of these reactions were of grade I intensity, for example, nausea, alopecia, and rash. Notably, both patients experienced transient hepatic impairment, with mild myocardial injury and thyroid injury occurring in case 1. However, with proper symptomatic management, these conditions completely resolved and did not recur during subsequent follow-up treatment. Importantly, neither of the patients displayed tertiary adverse reactions, and no adverse reactions necessitated discontinuation of the drug. These findings strongly suggest a high level of safety associated with the use of PD-1 inhibitors in the treatment of thymic squamous carcinoma.

Discussion among physicians from The Third Affiliated Hospital of Chongqing Medical University

Multidisciplinary team discussions were convened for the evaluation of both cases presented. Initial assessments revealed that neither patient was eligible for immediate surgical intervention post-diagnosis. Consequently, following deliberation within the multidisciplinary forums, a therapeutic regimen comprising cetuximab in conjunction with albumin-bound paclitaxel and carboplatin was administered. Subsequent to this treatment protocol, tumor downstaging was observed in both patients, thereby fulfilling the requirements for surgical candidacy. The controversy regarding the feasibility of surgical resection in such patients persists to date.

Department of Medical Oncology

Historically, the main treatments for thymic tumors have been surgery, radiotherapy, and chemotherapy. Based on current research findings, thymic tumors may derive survival benefits from the combination of immunotherapy and chemotherapy. However, it is important to note that thymic tumors may also be associated with autoimmune diseases, and the probability and severity of irAEs after immunotherapy are higher compared to other tumors. Therefore, after immunotherapy, we should monitor the occurrence of irAEs.

Department of Thoracic Surgery

Drawing parallels from thoracic surgery for common lung cancer, inoperable patients may undergo neoadjuvant immunotherapy in combination with chemotherapy to downstage the tumor, subsequently meeting the criteria for surgical resection. For our two cases, significant tumor regression was observed following preoperative immunotherapy and chemotherapy, without the incidence of severe immune-related adverse reactions, thus surgical intervention is recommended. Postoperatively, the decision to proceed with adjuvant immunotherapy or maintenance chemotherapy, as well as the potential need for supplemental radiotherapy, will be contingent upon the pathological assessment.

Several issues regarding the diagnosis and treatment of this patient were further discussed as follows

Question 1: Is type B thymoma suitable for immunotherapy?

Expert opinion 1: Dr. Fabrizio Minervini

Currently, there are no data supporting the use of immunotherapy in a neoadjuvant or adjuvant setting for patient with type B Thymoma.

Expert opinion 2: Dr. Georgina Planas

Thymic epithelial tumors are characterized by abnormal thymic epithelial cells with a dysfunctional expression of genes that participate in immune tolerance (AIRE, FEZF2 and MHC class II), as well as an altered thymic architecture. In this scenario, negative selection is impaired, allowing the release of autoreactive T-cells (28). This fact predisposes patients to autoimmunity and also to a high PD-L1 expression, because these autoreactive T-cells modify self-antigens expression on thymic epithelial cells by releasing interferon-gamma (IFN-γ) and upregulating PD-L1 expression (29).

On the other hand, immunotherapy has been proven to be effective in tumors with high expression of PD-L1 expression and high tumor mutational burden (TMB), both of which are the only two established biomarkers of response for ICIs (30).

Thymic tumors with a rich component of lymphocytes (types B1 and B2) are more prone to be associate to autoimmune disorders, either before or after the diagnosis. irAEs have been more frequent in recurrent type B thymomas treated with immunotherapy in different

trials (30). For example, Cho *et al.* reported that 5 (71%) of 7 patients were with thymomas and 4 (15%) of 26 patients were with TC reported grade 3 or greater irAEs (24).

For this reason, immunotherapy is not evoked in type B1/B2 thymoma due to the high rate of immune related adverse events and should not be delivered in an off-label setting without full disclosure of risks in the multidisciplinary tumor board (30).

Expert opinion 3: Dr. Katsuhiro Okuda

The use of immunotherapy for B thymoma is not suitable. Because the thymoma may be complicated with autoimmune diseases, such as myasthenia gravis, erythroblastic aplasia, agammaglobulinemia, etc. Furthermore, in type B thymoma, a portion of the tumor is occupied by infiltrated lymphocytes, which limits the effectiveness of immunotherapy.

Expert opinion 4: Dr. Naoki Ozeki

Thymomas are often associated with autoimmune diseases, and the use of PD-1 inhibitors can potentially stimulate the immune system, leading to life-threatening irAEs. However, a recent study has recognized immunotherapy as a relatively safe and moderately effective method for managing both B3 thymoma and thymic carcinoma (31).

Question 2: Why is thymic squamous carcinoma suitable for immunotherapy?

Expert opinion 1: Dr. Fabrizio Minervini

Thymic epithelial tumors express PD-1 and PD-L1 at high levels (ranging from 18% up to 100%) with significative differences between Masaoka stages and histological subtypes. Usually, a high expression of PD-1 and PD-L1 is observed in thymic carcinoma rather than thymoma.

The National Comprehensive Cancer Network Guidelines (version 2.2022) suggests pembrolizumab as a second-line therapeutic choice for patients with thymic carcinoma.

Expert opinion 2: Dr. Georgina Planas

Although thymomas have a high rate of PD-L1 expression, they have the lowest TMB of all adult cancers. Thymic carcinomas have a higher TMB and are lymphocyte-poor tumors, so they present a good response to immunotherapy with a lower proportion of irAEs (29,30).

Expert opinion 3: Dr. Katsuhiro Okuda

Thymic squamous cell carcinoma has similar characteristics to squamous cell of the lung, and there is no effective treatment other than complete surgical resection, so I think it is a good candidate for immunotherapy combined with chemotherapy. It may be a good indication, especially for cases with high expression of PD-L1 protein.

Expert opinion 4: Dr. Naoki Ozeki

Thymic squamous carcinoma shows high expression of PD-L1, which is linked to a positive response to PD-1 and PD-L1 antibodies. It is evident that ICIs are effective in treating thymic squamous carcinoma. However, although thymic squamous carcinoma has a lower tumor mutation burden compared to other tumors, it still carries some risk of autoimmune toxicity.

Question 3: What are the adverse effects that should be the focus of immunotherapy for patients with thymic cancer?

Expert opinion 1: Dr. Fabrizio Minervini

According to the current literature, immune related adverse events can occur in 15% to 60% of patients treated with ICIs. The adverse events can potentially affect any organ. The most common adverse effects are myasthenia gravis, myositis, myocarditis, erythema, diarrhea, thyroiditis, pneumonitis, and arthralgia.

Expert opinion 2: Dr. Georgina Planas

As noted in the review of Ballman *et al.*, ICIs appear to have a favorable safety profile in most patients with advanced thymic carcinoma. Common irAEs that are associated with pembrolizumab include fatigue, anorexia, chest wall pain, cough, diarrhea, and transaminitis, but approximately 15% of patients experienced severe irAEs including myositis, myocarditis, myasthenia gravis, and hepatitis. Therefore, there appears to be a poorly understood predilection for the development of muscle-related or neuromuscular autoimmune toxicity. In this setting, close follow-up and monitoring is imperative (29).

Expert opinion 3: Dr. Katsuhiro Okuda

As the adverse effects of immunotherapy for thymic cancer, we should be careful about irAEs, just as when treating tumors of other organs, including lung cancer. Due to the location and size of the tumor, it is assumed that there will be a feeling of tightness or a problem with circulation before treatment based, it is necessary to pay attention to the early detection of myocarditis which can be fatal if untreated.

Expert opinion 4: Dr. Naoki Ozeki

Immunotherapy for patients with thymic cancer should prioritize the management of the most severe adverse effects, such as myocarditis, myositis, myasthenia gravis, nephritis, and other significant consequences of autoimmune disorders.

Conclusions

Due to the relatively low prevalence of thymic squamous carcinoma, the availability of established treatment modalities remains limited. In contrast to thymoma, ICIs exhibit superior efficacy and heightened safety profiles in the management of thymic squamous carcinoma. Importantly, the incidence of severe and fatal adverse events associated with ICIs is significantly lower in cases of thymic squamous carcinoma than in those of thymoma. Therefore, the integration of immunotherapy with chemotherapy followed by surgical intervention represents a novel and promising therapeutic avenue for patients with stage III–IV thymic squamous carcinoma.

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Footnote

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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 Ethics Committee of The Third Affiliated Hospital of Chongqing Medical University and with the Helsinki Declaration (revised in 2013). Written informed consents were obtained from the patients for publication of this case report and accompanying images. Copies of the written consents are available for review by the editorial board of this journal.

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