Case Report

Immune checkpoint inhibitor myocarditis in thymic epithelial tumors: a case report and literature review

Ye Feng, Peng Zheng, Wei Zhang, Sheng Yang, Yundan You, Yong Chen, Yong Ye

Department of Intensive Care Unit, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China

Contributions: (I) Conception and design: Y Feng, Y Ye; (II) Administrative support: Y Ye; (III) Provision of study materials or patients: Y Feng, Y Ye; (IV) Collection and assembly of data: Y Feng; (V) Data analysis and interpretation: Y Feng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yong Ye, MA. Department of Intensive Care Unit, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuma Road, Fuzhou 350014, China. Email: yyong1031@126.com.

Background: Immunotherapy offers new hope for cancer patients but presents new medical challenges for healthcare workers in terms of the management of immune-related adverse events (irAEs). The clinical data of two patients with advanced thymoma (T) admitted to the Fujian Cancer Hospital who developed fulminant myocarditis after undergoing immunosuppressant therapy were analyzed retrospectively, and the relevant literature was reviewed. This study aims to examine treatment of thymic epithelial tumors (TETs)-associated immune myocarditis.

Case Description: An online search was conducted to retrieve relevant full-text articles, and the selected articles were assessed. In total, 13 articles, comprising the data of 113 patients, were included in an analysis to evaluate the efficacy of immunotherapy. Of the 113 patients, 19 had T and 94 had thymic carcinoma (TC). Of the 19 patients with T, 10 (52.6%) achieved a partial response (PR), 8 (42.1%) had stable disease (SD), and 1 (5.3%) had progressive disease (PD). Of the 94 patients with TC, 1 (1.1%) achieved a complete response (CR), 20 (21.3%) achieved a PR, 51 (54.3%) had SD, and 22 (23.4%) had PD. Five articles reported that fulminant myocarditis developed in nine thymic epithelioma patients who were treated with immunosuppressive agents. Two TC patients who presented with fulminant myocarditis were treated with high-dose corticosteroid therapy and underwent pacemaker insertion; none of the patients died of immune myocardial toxicity. However, of the seven T patients who received high-dose corticosteroid therapy and immunoglobulin therapy, and underwent pacemaker implantation, three survived and four died.

Conclusions: Immunotherapy has shown promising results in the treatment of patients with refractory or relapsed TETs. Due to their susceptibility to paraneoplastic autoimmunity, TET patients are at a higher risk of developing severe irAEs than patients with other types of cancer. Given the relatively high morbidity and mortality of irAEs, the administration of immune checkpoint inhibitors (ICIs) to treat TETs should be balanced against the clinical response and the precipitation of potentially severe irAEs.

Keywords: Thymic epithelial tumors (TETs); immunotherapy; immune checkpoint inhibitor myocarditis (ICI myocarditis); efficacy; case report

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Introduction

Thymic epithelial tumors (TETs), which can be subdivided into thymomas (Ts) and thymic carcinomas (TCs), are the most prevalent malignancies of the anterior mediastinum in adults, and have an incidence of approximately 1.5 cases per million people (1). Due to its rapid invasiveness compared with that of T, the prognosis of TC is poor (2).

TETs are only potentially curable through total surgical

excision; however, palliative chemotherapy is indicated for locally advanced or metastatic disease. First-line platinum-based combination chemotherapy is effective against TETs (3,4). Patients with TETs who do not respond to platinum-based chemotherapy have limited treatment options; however, a few prospective studies have investigated potential therapies for these patients. Previous research showed that conventional chemotherapy and targeted therapies have shown modest anti-tumor activity in patients with refractory or recurrent TETs (5-7). Tumor mutation burden (TMB) is the number of mutations that exist within a tumor (8,9). TETs have the lowest tumor TMB of all adult malignancies, making it difficult to identify new drug targets. To overcome the challenges associated with drug development for relapsed or resistant TETs, it is necessary to contemplate the use of novel approaches. The activation of anti-tumor immunity is an attractive treatment option (10). The thymus gland is essential for the formation of immune tolerance. Thus, the unique physiology of the thymus influences the potential risk-benefit ratio of immunotherapy for TETs (11,12).

Programmed cell death ligand 1 (PD-L1) expression in tumor cells, microsatellite instability, and TMB are the current predictive factors used to identify patients who are likely to respond to immune checkpoint inhibitors (ICIs) (13-15). Previous studies have shown that PD-L1 is expressed in normal thymic cortex cells, and is highly expressed in TET (16-19). Such findings support the use of immunotherapy. These preliminary studies suggest that antibodies targeting programmed death-1 (PD-1) and/or PD-L1 are promising immunotherapeutic agents against relapsed or refractory TETs (12,20-22). Cancer immunotherapy is an emerging field, and several clinical trials have provided evidence that immunotherapy produces anti-tumor activity and durable responses in a subset of patients with TETs (23-26).

Early clinical trial results on the use of ICIs in various types of cancer have demonstrated clinical efficacy, albeit the incidence of serious immune-related adverse events (irAEs) is high (27). TETs, primarily Ts, cause immune deficiency and autoimmune diseases due to the disruption of thymic function, including myasthenia gravis, pure red cell aplasia, and Good's syndrome (28,29). Additionally, the increased incidence of irAEs, especially myocarditis, it is a novel discovery with low case ascertainment. Further, the effects are not at all subtle—these patients often present with syncope, severe myositis or myasthenic syndrome with a troponin in the thousands. Currently, ICIs have been shown to produce anti-tumor responses and promote the survival of patients with various types of cancer; however, only a few large-scale clinical trials have been performed to evaluate the efficacy and safety of ICI treatment in TETs.

Herein, we report cases of patients with TETs who developed fulminant cardiotoxicity after receiving immunotherapy and were diagnosed and managed at the Fujian Cancer Hospital. A review of the relevant literature is also conducted. This provides evidence for the efficacy of immunotherapy in this rare malignancy and the prognosis of fulminant ICI myocarditis. As this type of malignant tumor can induce the development of an autoimmune disease, the benefits and risks should be carefully considered when using ICIs. We also review ongoing efforts to mitigate the risk of myocarditis in TET patients receiving ICIs and provide our thoughts on whether immunotherapy is a viable treatment option for thymic tumors. We present this article in accordance with the CARE and PRISMA reporting checklists (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2212/rc).

Highlight box

Key findings

- Immunotherapy has shown promising results in treating refractory or relapsed thymic epithelial tumors (TETs).
- In treating TET patients with immunotherapy, the clinical benefits must be balanced against the precipitation of potentially serious adverse events (AEs), especially immune checkpoint inhibitor (ICI) myocarditis.

What is known, and what is new?

- The thymus gland is essential for the formation of immune tolerance. The unique physiology of the thymus influences the potential risk-benefit ratio of immunotherapy for TETs.
- Immunotherapy has shown promising results in treating patients with refractory or relapsed TETs. Clinicians should carefully monitor the occurrence of ICI myocarditis. This is particularly important given its early onset, non-specific symptomatology, and fulminant progression.

What is the implication, and what should change now?

- Immunotherapy for TETs must balance the induced clinical response against the precipitation of potentially serious AEs, especially ICI myocarditis.

Case presentation

A 45-year-old man with a history of metastatic T and pleural and lung metastases received sintilimab (200 mg)

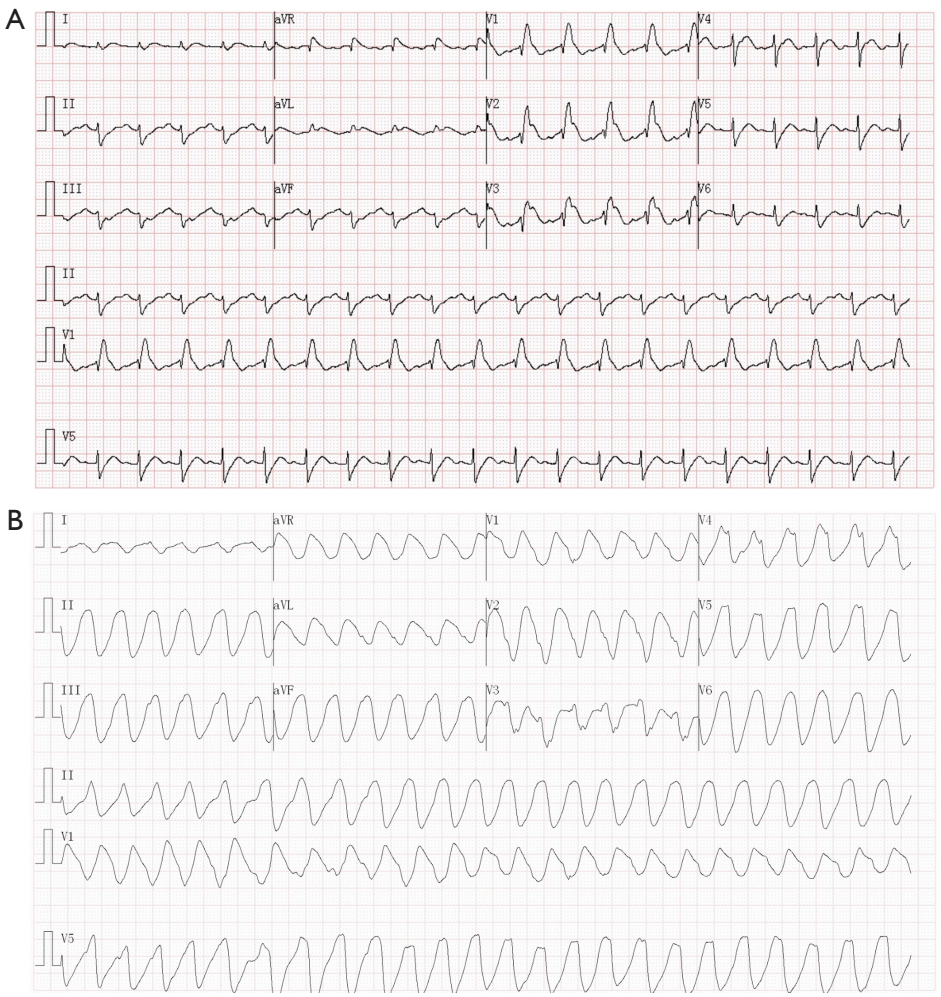

Figure 1 Clinical ECG. (A) Abnormal ST-T, complete right bundle branch block, and extensive ischemic changes on ECG. (B) Emergency ECG showed ventricular flutter. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot; ECG, electrocardiography.

plus chemotherapy after the failure of first-line platinum-based combination chemotherapy. The patient had no history of autoimmunity. PD-L1 expression was positive in 20% of the tumor cells. Eleven days after the initial administration of sintilimab, the patient experienced chest tightness, shortness of breath, and weakness. He showed abnormal ST-T, complete right bundle branch block, and extensive ischemic changes on electrocardiography (ECG) (*Figure 1A*), and rising levels of creatine phosphokinase and troponin T (TnT), and was eventually diagnosed with myocarditis syndrome. He was initially treated with methylprednisolone 560 mg/once daily (qd). On the fourth day of hospitalization, he developed acute respiratory failure and was transferred to the intensive care unit (ICU). He was initially placed on noninvasive positive-pressure ventilation but was eventually intubated. The patient continued to receive large supplemental doses of corticosteroids and intravenous immunoglobulin. On the second day of ICU admission, he experienced cardiac arrest and received cardiopulmonary resuscitation. He received b-blockers, antiarrhythmics, and large supplemental doses of corticosteroids and intravenous immunoglobulin as treatment for acute auto ICI myocarditis caused by sintilimab; however, despite aggressive management, the patient developed decompensated heart failure and ventricular arrhythmia. Emergency ECG showed ventricular flutter (*Figure 1B*). He also showed persistent troponin elevation. He died 5 days later after being taken to the ICU.

The second patient was a 58-year-old man who had recurrent and metastatic mixed B1/B2 T. The patient had failed multiple lines of chemotherapy. He had a history of myasthenia gravis, and he had no history of autoimmunity or cardiovascular events. Toripalimab was administered after disease progression; 11 days later, he experienced acute chest tightness and shortness of breath. Corticosteroids [250 mg/every 12 h (q12h)] were administered around 3 days after the symptoms first appeared, but his condition did not improve. Thus, he was admitted to the ICU and intubated. The biochemical analysis showed elevated levels of the cardiac biomarker TnT 1,111 pg/mL (reference value, <14 pg/mL), brain natriuretic peptide (BNP) 2,391 pg/mL (reference value, <300 pg/mL), and creatine kinase MB (CK-MB) 230.7 ng/mL (reference value, <6.22 ng/mL). ECG (*Figure 2A*) showed abnormal T waves but echocardiography revealed acute heart failure with diffuse hypokinesia. Immunotherapy led to a presumptive diagnosis of myocarditis based on this clinical feature. As the patient was intubated, cardiovascular magnetic resonance (CMR) imaging was not performed. The patient's relatives refused an endocardial biopsy due to the invasive nature of this procedure. The patient was not successfully weaned from mechanical ventilation. The patient was diagnosed with myasthenia with positive anti-acetylcholine receptor antibodies. The muscle biopsy result was negative (Figure S1). Corticosteroids (250 mg/q12h) and a course of immunoglobulin (400 mg/kg for 5 days) were administered, but the patient showed very little improvement. As a result, the patient received two more weekly administrations of infliximab and then started showing signs of clinical improvement. After applying various active treatments, the patient survived. *Figure 2B*,*2C* show the management processes and the change in the myocardial injury marker. One year after the initial dose of toripalimab, the patient showed stable disease (SD) on routine surveillance.

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 (as revised in 2013). Written informed consent was unable to obtain from the patients or their families, though we have made the best efforts to contact the relative. The article has been sufficiently anonymized to cause no harm to the patients or theirs families.

Information and search strategy

On August 22, 2021, the PubMed database was systematically searched using the following terms: "checkpoint blockade" or "checkpoint inhibitor" or "checkpoint inhibitors" or "immunotherapy" or "immunotherapies" or "PD-1" or "PD-L1" or "LAG-3" or "pembrolizumab" or "nivolumab" or "camrelizumab" or "sintilimab" or "toripalimab" or "tislelizumab" or "atezolizumab" or "durvalumab" and "thymoma" or "thymic carcinoma" or "thymic epithelial tumor" or "thymic tumor". The reference lists of the selected articles were also manually reviewed to identify additional cases. A total of 1,160 articles were retrieved, of which 16 met the inclusion criteria. The included articles described 113 patients with thymic epithelioma and evaluated the efficacy of PD-1 inhibitors. Of the 16 articles, five described nine patients who were diagnosed with myocarditis. All the articles that met the inclusion criteria were carefully read, including the full text and the reference list, and the related literature was also searched.

Eligibility criteria

To responds to the predefined population, intervention, control, and outcomes (PICO) question, a literature search was conducted to patients who received ICIs for the treatment of TETs (T and TC).

(I) Is it available to achieve the outcomes of TETs patients who received ICI as a second- or third-line therapy?
   (i) Population: patients who were diagnosed with TETs;
   (ii) Intervention: patients treated with ICIs [PD-1, PD-L1, or cytotoxic T-lymphocyte antigen-4 (CTLA-4)];
   (iii) Complication: patients treated with ICIs developed adverse events (AEs);
   (iv) Outcomes: death, progressive disease (PD), SD, a partial response (PR), and a complete response (CR).

(II) Is it controllable when TETs patients who received ICIs were diagnosed with myocarditis?
   (i) Population: patients who were diagnosed with TETs;
   (ii) Intervention: patients treated with ICIs;
   (iii) Complication: patients treated with ICIs developed myocarditis;
   (iv) Outcomes: patients died of myocarditis.

Study selection and data extraction

Two evaluators independently selected the articles and extracted the relevant information according to the

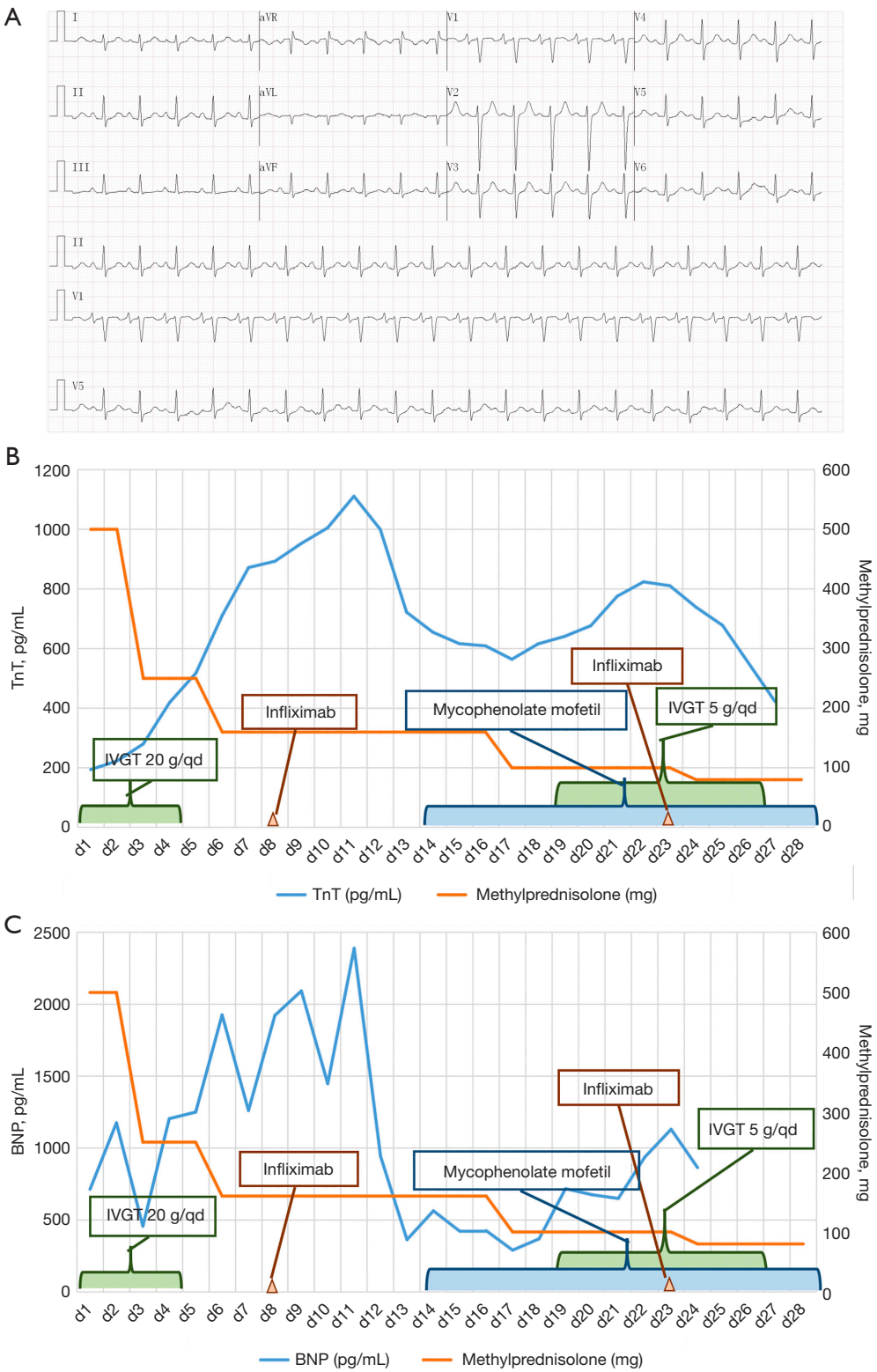

Figure 2 The changes of ECG and myocardial injury marker. Abnormal ECG picture (A) ECG showed abnormal T waves. (B,C) The management processes and the change in the myocardial injury marker. aVR, augmented vector right; aVL, augmented vector left; aVF, augmented vector foot; TnT, troponin T; IVGT, intravenous immunoglobulin; qd, once daily; BNP, brain natriuretic peptide; ECG, electrocardiography.

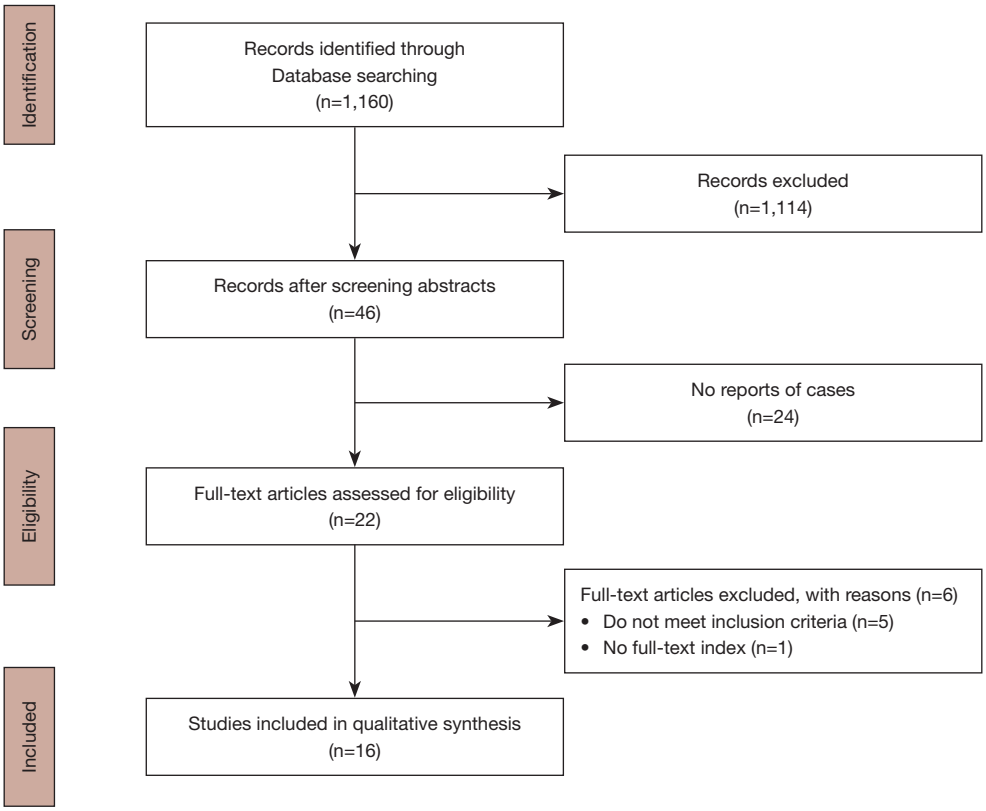

Figure 3 Flow diagram of the study selection process.

inclusion criteria. If the opinions of the two evaluators differed, a third party was consulted.

The following information was extracted from the literature on patients with thymic epithelioma who were treated with immunosuppressants and developed grade (G)4 ICI myocarditis: name of first author, article type, drug name, previous history of autoimmune diseases, other adverse immune reactions, time of occurrence of ICI myocarditis, treatment scheme of ICI myocarditis, and outcome (death due to ICI myocarditis) (Tables S1,S2).

The following information was extracted from the literature related to efficacy evaluations of immunosuppressants in patients with thymic epithelioma: name of the first author, article type, drug name, previous history of autoimmune diseases, efficacy evaluation, adverse immune reaction, and outcome (death due to adverse immune reaction) (Tables S3-S6).

Identification and selection of studies

Figure 3 provides a flowchart of the study selection process. In total, 1,160 publications were retrieved. Of the 1,160 publications, 46 met the inclusion criteria after the title screening. Of these 46 articles, 24 were reviewed and were excluded after reading the abstracts, as they did not contain case reports, and 22 were subjected to the full-text screening. Of the 22 articles, six were excluded (five because they did not meet the inclusion criteria, and one because it was not indexed in PubMed). The qualitative synthesis included all 16 papers, within the case reports and clinical trials. The included studies were published between the inception of the database and August 22, 2021.

Study selection results

A tool was used to screen the titles and abstracts of the articles to identify the research with potential. The articles were retrieved online, and the full text of the selected articles was evaluated to determine if they met the inclusion criteria.

Tumor control was described in 13 reports, comprising 113 participants. All the patients were diagnosed with cancer

and treated with ICIs as a single or combination therapy. Patient follow-up varied widely, as some did not undergo follow-up after hospital discharge, while others underwent follow-up for several months. In total, 94 patients were diagnosed with TC in 10 studies (23-26,30-35), and 19 were diagnosed with T in six studies (23,25,31,36-38). Of the 10 studies with TC patients, five were clinical trials, and the remaining were either case reports or retrospective analyses. Of the 94 TC patients treated with one or more ICIs, one achieved a CR, 20 achieved a PR, 51 had SD, and 22 had PD. Of the six studies with T patients, two were clinical trials and four were case reports or retrospective analyses. Of the 19 patients diagnosed with T, 10 achieved a PR, eight had SD, and one had PD.

Myocarditis was diagnosed based on the results of a cardiac biomarker test, ECG, CMR imaging or computed tomography of the heart, cardiac catheterization, and endomyocardial biopsy (EMB). Nine patients were identified as having ICI myocarditis in five articles (23,24,39-41). The patients had either T (n=7) or TC (n=2). Four patients had fatal outcomes caused by myocarditis. Four of the seven patients in the T group treated with high-dose steroids and immunosuppressive agents died. Three patients showed improved clinical conditions after steroid therapy, pacemaker insertion, and immunosuppressive treatment. Two TC patients who received steroids and underwent pacemaker insertion survived.

Discussion

ICIs may enhance patients' tumor-specific immune responses and restore anti-tumor immune surveillance, creating a window of opportunity for cancer treatment. The emergence of ICIs has modified the therapeutic landscape of oncology (42). PD-L1 expression in solid tumors has been identified as an ideal biomarker for predicting the efficacy of anti-PD-1/PD-L1 therapy. PD-L1 is highly expressed in TETs, which indicates the suitability of anti-PD-1/PD-L1 treatment. Based on this hypothesis, some clinical trials (23,26) have assessed the effectiveness and security of anti-PD-1/PD-L1 agents in patients with TETs who experienced disease progression following at least one line of platinum-based chemotherapy.

For the literature review, an extensive search of the PubMed database was conducted to retrieve relevant articles published in English, and the data of 19 patients with T and 94 patients with TC were collected. Approximately 94.7% of the total patients (18/19) with T and 76.6% of the total patients (72/94) with TC did not show disease progression, indicating that ICIs are potent immunosuppressive agents for TETs. In addition, some ongoing clinical trials have evaluated the efficacy of ICIs in patients with TET. PECATI (https://clinicaltrials.gov/, NCT04710628), an open-label, single-arm, multicenter study, evaluated the clinical outcomes of pembrolizumab in combination with lenvatinib in 43 patients with TETs; the study was initiated in 2021. Ongoing clinical trials are evaluating the efficacy of ICIs alone (avelumab, nivolumab, and pembrolizumab) or in combination with other drugs (pembrolizumab with epacadostat or sunitinib) in patients with TETs. Patients with TETs eagerly await the results of these trials, which will provide additional information about the hazards and advantages of using ICIs alone or as part of a combination strategy. The efficacy of ICIs in the treatment of TETs requires further investigation.

Due to their susceptibility to paraneoplastic autoimmunity, TET patients are at a higher risk of developing severe irAEs than patients with other types of cancer. T contains a substantial number of cluster of differentiation (CD)41/CD81 double-positive T cells, which suggests that a breakdown in the thymus medullary selection process in this type of TET may be responsible for the discharge of autoreactive T cells (29). Many types of Ts are abundant in autoantigen-specific T cells; a disruption in the composition of the circulating T-cell fraction through the export of intratumorous T cells could trigger the development of paraneoplastic autoimmune disease in patients with T (43). A particular pathophysiology may result in TETs with a higher incidence of complications (12).

The two patients with T reported in this article developed explosive ICI myocarditis shortly after the initial use of immunosuppressants. Neither of the patients had a history of cardiovascular disease. Each patient received either sintilimab or toripalimab. Nine thymic epithelial patients identified in the literature review developed severe ICI myocarditis after one to two cycles of immunosuppressive therapy. All four of nine patients reported severe ICI myocarditis within 30 days of the initial treatment of immunosuppressants. Mahmood's study on myocarditis reported similar results (44). A previous investigation of 35 patients with ICI-associated myocarditis from an eight-center institutional registry found that the median time of symptom onset was 34 days after starting ICI therapy [interquartile range (IQR), 21–75 days]. Fan's study based on the Food and Drug Administration's Adverse Event Reporting System, which was conducted

from January 2004 to June 2018, reported that myocarditis caused by treatments with ICIs occurred after a single cycle of several ICI monotherapies, including pembrolizumab, nivolumab, and atezolizumab, and had a median time to onset of 22 (IQR, 10.25–64), 32 (IQR, 16–77), and 28 (IQR, 8–89) days, respectively (45). In clinical practice, fulminant myocarditis mostly develops after one to two doses of ICI (46,47). Additionally, patients may experience late-onset fulminant myocarditis more than 1 year after immunotherapy (48). It has been previously suggested that ICI myocarditis occurs in the following two forms: (I) a high-grade form with enhanced inflammatory cell infiltration; and (II) a more aggressive clinical course and a low-grade form with less degree of inflammatory cell infiltration and a more indolent clinical course (49).

Given its early onset, non-specific symptomatology, and fulminant progression, clinicians should closely monitor the occurrence of immune-mediated myocarditis. To date, no study has described a strategy that can be used to monitor the development of myocarditis. Clinical findings and previous studies have indicated that it is necessary to monitor the baseline ECG and the troponin levels weekly (from weeks 1 to 4) in patients receiving immunotherapy (44,45). Further, myocarditis can occur after the continuous use of immunotherapy; thus, vigilance must be maintained, even if irAEs are not observed. Among the five patients diagnosed with myocarditis in two clinical trials, none died due to myocarditis during the trial period. Care providers often send such patients to the clinical trial management department to determine the appropriate immunosuppressants.

Two patients with T reported in our study were administered a high-dose pulse of glucocorticoid and immunoglobulin immediately after the diagnosis of ICI myocarditis. A patient with T showed rapid progression, developed malignant arrhythmia, and eventually died of cardiac and respiratory arrest. Another patient survived and demonstrated SD after aggressive treatment. Among the nine thymic epithelioma patients whose data were retrieved from PubMed, seven had T. Four of these patients died of severe ICI myocarditis, and the mortality risk was 57.1%. In a multicenter registry comprising the data of individuals who developed myocarditis due to ICIs, 16 of the 35 patients diagnosed with myocarditis experienced significant adverse cardiovascular events during a median follow-up period of 102 days (44). Among these patients, six individuals succumbed to cardiovascular-related causes, three developed cardiogenic shock, four experienced cardiac arrest, and three suffered from complete heart block. These findings emphasize the potentially life-threatening nature of this irAE and emphasize the crucial need for vigilant monitoring. Salem *et al.* conducted an observational, retrospective pharmacovigilance study and found that patients with ICI myocarditis often have an unfavorable prognosis, with a case fatality rate of 50%, and fatalities occurring most frequently in those receiving ICI combination therapy (65.5%) (47). Moslehi *et al.* examined the VigiBase and the World Health Organization global database of individual case safety reports and identified 101 patients with fulminant myocarditis in 2017, of whom, 46 died (46). Due to the challenges of establishing the diagnosis in standard clinical settings, the incidence of non-fatal myocarditis is likely greater than that of the actual diagnosis.

Currently, no standard treatment regimen has been established for irAEs in the literature or guidelines. Clinicians usually follow the treatment principles that are similar to those used in the management of primary autoimmune diseases. Corticosteroids, which have a promising curative effect, are commonly recommended as a first-line treatment in several guidelines. However, if steroid treatment alone is not effective, other immunosuppressive agents should be used. Fulminant myocarditis usually requires second-line therapy. High-dose glucocorticoids, mycophenolate mofetil, immunoglobulin, and infliximab were used in our successful case. They had a positive effect on the reduction of troponin levels. The immunosuppressive strategies reported in the incorporated research studies were high-dose glucocorticoids, immunoglobulin, mycophenolate mofetil, and rituximab. These treatments are effective and significantly improve patient prognosis.

This study had some limitations. First, we present two cases of severe ICI myocarditis. A comprehensive literature search for relevant publications was performed; however, some scenarios had an unclear risk of selection bias. Notably, cases with mild asymptomatic presentations, characterized solely by biochemical markers indicative of myocarditis, might not have been documented, which could have potentially led to their underreporting. A similar condition might be anticipated in individuals experiencing severe instances of ICI myocarditis, which, for various reasons, have yet to be documented. Both conditions could potentially introduce selection bias. Secondly, follow-up in all study patients varied widely; some patients were not followed-up after they were discharged, while others were followed-up for several months. This made it difficult to

assess the long-term effects of immunosuppressive regimens on cardiac function in some cases. Finally, the diagnostic evidence was based on the clinical history, past medical history, physical examination, serological laboratory tests, ultrasound findings, and auxiliary examinations in our study. Myocarditis was defined as the absence of CMR and EMB findings to support a definitive diagnosis (50,51).

Conclusions

ICIs have shown promising clinical efficacy in the treatment of refractory or recurrent TETs, which are often accompanied by side effects. The safety profile of PD-1/PD-L1 therapy is noteworthy. Immunotherapy with TETs must balance the induced clinical response against the precipitation of potentially serious AEs, especially ICI myocarditis. Given that they can be monitored and prevented, immunotherapy should be applied while mitigating the risks mentioned in the article. Clinicians should fully evaluate the related benefits and risks of using ICIs. If possible, immunotherapy for TET patients should be administered in the context of clinical trials. Thus, clinical trials should be conducted in the future to confirm the efficacy of immunotherapy; if these trials show promising results, the therapy can be extended to more patients.

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Footnote

Reporting Checklist: The authors have completed the CARE and PRISMA reporting checklists. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2212/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2212/coif). The authors have no 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 (as revised in 2013). Written informed consent was unable to obtain from the patients or their families, though we have made the best efforts to contact the relative. The article has been sufficiently anonymized to cause no harm to the patients or theirs families.

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Supplementary

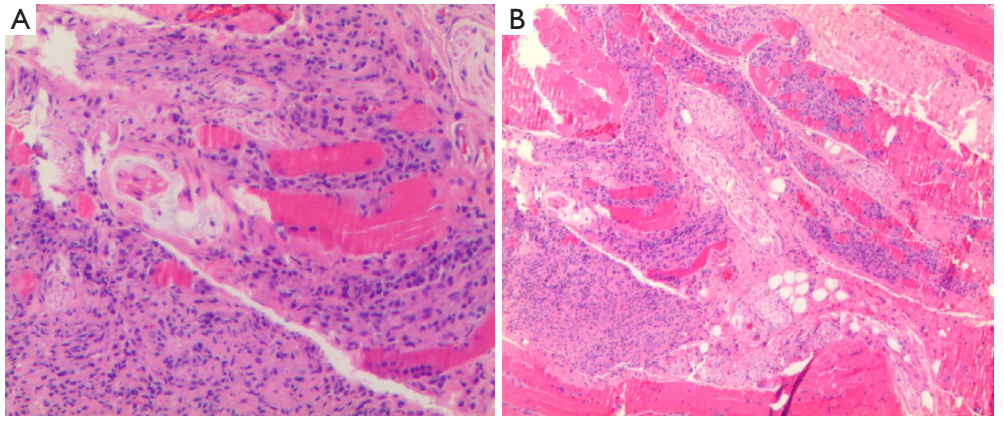

Figure S1 Muscle biopsy with hematoxylin-eosin staining [(A) ×100; (B) ×40]: (trachea and neck muscle) spindle cell proliferation (with a mild shape and no obvious nuclear division) was observed in the skeletal muscle. Combined with the immunohistochemistry results, the possibility of proliferative myositis was considered.

Table S1 Clinical trial of PD-1/PD-L1 inhibitors for Ts and TCs about ICI myocarditis

Author	Number	Type	Drugs	Previous autoimmune disease	CMR or EMB	Grade	Type of other irAE	Time when irAE occurred	Treatment	Outcome (whether deaths due to toxicity)
Giaccone *et al.* (24)	2	TC	Pembrolizumab	No	NA	4	Polymyositis, myositis	2 cycles	Glucocorticoid, pacemaker	No
		TC	Pembrolizumab	No	NA	4	Polymyositis	2 cycles	Glucocorticoid, pacemaker	No
Cho *et al.* (23)	3	T (B2)	Pembrolizumab	Myasthenia	NA	4	Myasthenia	1 cycle	Glucocorticoid, immunoglobulin	No
		T (B2)	Pembrolizumab	No	NA	4	Autoimmune hepatitis, thyroiditis	2 cycles	Glucocorticoid, immunoglobulin	No
		T (B2/B3)	Pembrolizumab	No	NA	4	No	2 cycles	Glucocorticoid, immunoglobulin	No

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; T, thymoma; TC, thymic carcinoma; ICI, immune checkpoint inhibitor; CMR, cardiovascular magnetic resonance; EMB, endomyocardial biopsy; irAE, immune-related adverse event; NA, not available.

Table S2 Nonrandomized clinical trial of PD-1/PD-L1 inhibitors for Ts and TCs about ICI myocarditis

Author	Number	Gender	Age (years)	Type	Drugs	Previous autoimmune disease	CMR or EMB	Grade	Type of other irAE	Time when irAE occurred	Treatment	Outcome (whether deaths due to toxicity)
Hyun *et al.* (39)	1	F	45	T (B2)	Pembrolizumab	Chronic hepatitis B	No	4	Oscular MG, hepatic dysfunction	1 cycle	Glucocorticoid pulse therapy	Yes
Chen *et al.* (40)	1	M	43	T (B3)	Nivolumab	No	CMR	4	N0	1 cycle	Glucocorticoid, pacemaker, IVIG	Yes
Konstantina *et al.* (41)	2	F	58	T (B2/B3)	Pembrolizumab	Ocular myasthenia gravis	No	4	Stevens Johnson hepatis dysfunction	1 cycle	Mycophenolate mofetil	Yes
		F	30	T (B3)	Pembrolizumab	No	No	4	Myositis	1 cycle	Glucocorticoid, IVIG, rituximab	Yes

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; T, thymoma; TC, thymic carcinoma; ICI, immune checkpoint inhibitor; CMR, cardiovascular magnetic resonance; EMB, endomyocardial biopsy; irAE, immune-related adverse event; F, female; MG, myasthenia gravis; M, male; IVIG, intravenous immunoglobulin.

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Table S3 Clinical trial of PD-1/PD-L1 inhibitors for Ts about curative effect evaluation

Author	Number	Drugs	Previous autoimmune disease	Curative effect evaluation	Whether irAE occurs	Outcome (whether deaths due to toxicity)
Rajan *et al.* (25)	7	Avelumab	No	cPR	Yes	No
		Avelumab	No	SD	Yes	No
		Avelumab	No	uPR	Yes	No
		Avelumab	No	PR	Yes	No
		Avelumab	No	cPR	Yes	No
		Avelumab	No	SD	No	–
		Avelumab	No	PD	No	–
Cho *et al.* (23)	7	Avelumab	Myasthenia	PR	Yes	Yes
		Avelumab	Myasthenia	PR	Yes	No
		Avelumab	No	SD	Yes	No
		Avelumab	No	SD	Yes	No
		Avelumab	No	SD	Yes	No
		Avelumab	No	SD	No	–
		Avelumab	No	SD	No	–

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; T, thymoma; irAE, immune-related adverse event; cPR, confirmed PR; PR, partial response; SD, stable disease; uPR, unconfirmed PR; PD, progressive disease.

Table S4 Nonrandomized clinical trial of PD-1/PD-L1 inhibitors for Ts about curative effect evaluation

Author	Number	Age (years)	Drugs	Previous autoimmune disease	Curative effect evaluation	Whether irAE occurs	Outcome (whether deaths due to toxicity)
Zander *et al.* (36)	1	49	Pembrolizumab	No	PR	Yes	No
Ak *et al.* (31)	2	52	Nivolumab	No	PR	No	–
		43	Nivolumab	No	SD	No	–
Argentiero *et al.* (37)	1	42	Pembrolizumab	No	PR	Yes	Yes
Shen *et al.* (38)	1	53	Pembrolizumab	No	PR	No	–

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; T, thymoma; irAE, immune-related adverse event; PR, partial response; SD, stable disease.

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Table S5 Clinical trials of PD-1/PD-L1 inhibitors for TCs about curative effect evaluation

Author	N	Drugs	Previous autoimmune disease	Curative effect evaluation	Whether irAE occurs	Outcome (whether deaths due to toxicity)
Mizugaki *et al.* (35)	1	Atezdizumab	No	SD	Yes	No
Rajan *et al.* (25)	1	Avelumab	No	SD	No	–
Katsuya *et al.* (26)	15	Nivolumab	No	SD/PD: 11/4	Yes	No
Giaccone *et al.* (24)	40	Pembrolizumab	No	CR/PR/SD/PD: 1/8/21/10	Yes	No
Cho *et al.* (23)	26	Pembrolizumab	No	PR/SD/PD: 5/14/7	Yes	No

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; TC, thymic carcinoma; irAE, immune-related adverse event; SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response.

Table S6 Nonrandomized clinical trial of PD-1/PD-L1 inhibitors for TCs about curative effect evaluation

Author	Number	Drugs	Previous autoimmune disease	Curative effect evaluation	Whether irAE occurs	Outcome (whether deaths due to toxicity)
Yang *et al.* (30)	1	Nivolumab	No	PR	Yes	No
Ak *et al.* (31)	4	Nivolumab	No	SD	No	–
		Nivolumab	Myasthenia gravis	PR	Yes	No
		Nivolumab	No	PR	Yes	No
		Nivolumab	No	PR	No	–
Wong-Chong *et al.* (32)	1	Pembrolizumab	No	PD	No	–
Cafaro *et al.* (33)	1	Pembrolizumab	No	SD	No	–
Uchida *et al.* (34)	4	Nivolumab	No	PR	No	–
		Nivolumab	No	PR	No	–
		Nivolumab	No	PR	No	–
		Nivolumab	No	SD	Yes	No

PD-1, programmed death-1; PD-L1, programmed cell death ligand 1; TC, thymic carcinoma; irAE, immune-related adverse event; PR, partial response; SD, stable disease; PD, progressive disease.

https://dx.doi.org/10.21037/tcr-23-2212