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A case of acute myocarditis induced by PD-1 inhibitor (sintilimab) in the treatment of large cell neuroendocrine carcinoma

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ABSTRACT

The combination of Sintilimab with pemetrexed/platinum has become the first-line treatment for non-squamous non-small-cell lung carcinoma (NSCLC). Here, we report a patient with metastatic large cell neuroendocrine carcinoma (LCNEC) treated with Sintilimab for five cycles who developed shortness of breath after activity. The level of creatine kinase (CK), creatine kinase-MB (CK-MB) and cardiac troponin T (cTnT) were significantly increased. The cardiac MR suggested that heart function was slightly decreased. Considering that the patient did not take any illicit drugs, without history of autoimmune disease, coronary heart disease, arrhythmia, or chronic heart failure, we diagnosed the patient with Sintilimab-induced myocarditis. The symptoms alleviated after rapid use of glucocorticoids. Myocarditis is a rare immune-related adverse events (irAEs), especially myocarditis induced by programmed cell death receptor-1 (PD-1) inhibitor in the treatment of LCNEC.

1. Introduction

In recent years, immune checkpoint inhibitors (ICIs) had been widely used in clinical anti-tumor therapy. However, with the application of programmed cell death receptor 1/programmed cell death ligand 1 (PD-1/PD-L1) blockers in clinical trials and applications worldwide, an increasing number of adverse events have been reported. PD-1 antibodies block the negative regulatory signals of T cells to relieve immunosuppression and enhance the anti-tumor effect of T cells. At the same time, they may also abnormally enhance the normal immune response, leading to imbalance in immune tolerance, so that normal tissues show autoimmune inflammatory reactions, called immune-related adverse events (irAEs). And the irAEs could occur in multiple organs including the skin, digestive tract, liver, endocrine glands, lung and other organs [1–3]. Sintilimab has been proven to be effective in locally advanced head and neck tumors, esophageal cancer, liver cancer and other solid tumors and was approved for use in China [4–6]. Currently, reports of immune-related heart injury are very limited. Here, we report a case of myocarditis induced by Sintilimab in the treatment of LCNEC.

1.1. Case presentation

On April 20, 2020, a 52-year-old male patient was hospitalized due to repeated cough for 2 months. The patient denied a history of

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autoimmune diseases, diabetes, hypertension, coronary disease, arrhythmia, chronic heart failure or smoking. Enhanced CT showed a mass at the left hilar with a cross-section of about 63 mm × 62 mm, and metastases in bilateral adrenal glands were observed. LCNEC was confirmed by neuroendocrine immunohistochemical staining in a biopsy specimen (Fig. 1A–C). Combined with the above examination results, the patient was diagnosed as LCNEC (cT3N3M1-Stage IVB), which has no indication for surgery. Genetic testing revealed the tumor to be BRAF-positive, ALK- and EGFR-negative (Illumina, Inc., CA, USA). Since the patient refused BRAF inhibitor therapy for financial reasons, chemotherapy was selected as the first-line treatment for advanced lung cancer according to National Comprehensive Cancer Network (NCCN) guidelines. In the first cycle of chemotherapy, the patient was treated with docetaxel 75 mg/m2 (day 1) plus carboplatin AUG 5 (day 1 and 2). Thereafter, the patient was supplemented with Sintilimab (200 mg) immunotherapy for a total of five courses because of PD-L1 tumor proportion score (TPS) of 80% by immunohistochemistry (IHC) (assessed by the Dako PD-L1 IHC 22C3 Pharmdx kit, Fig. 1D). The chest-enhanced CT was rechecked after two courses of therapy and the results indicated that the tumor volume had been significantly reduced to 29 mm × 27 mm (shrinkage about 46%) after the fourth course, which was evaluated as partial remission (Fig. 2). The patient had shown no previous irAEs. However, 4 months later, one week after the 5th cycle of chemotherapy and immunotherapy, the patient experienced shortness of breath, loss of appetite and weight at presentation. On admission, the patient not only denied the use of illegal drugs or herbs, but also denied that he had a fever, cough or other symptoms. Physical examination showed T: 36.5 °C; R: 20/min, regular; BP: 156/98 mmHg; SpO2: 98%. Breathing sounded normal in both lungs, without moist or dry rales. Heart rate was 115 bpm with normal rhythm. There were no extra cardiac sounds or pathological murmurs, and no pericardial friction. There was also no edema in either lower limb. Biochemical functions indicated that the CK (4977 U/L, Reference range 41–186 U/L) and CK-MB (526 U/L, Reference range 0–24 U/L) were significantly increased (Fig. 3A and B). We then immediately checked the level of the cTnT, which was significantly increased to 2230 ng/L (Reference range 0–14 ng/L) (Fig. 3C). N-terminal-pro B type natriuretic peptide (NT-ProBNP) was only slightly elevated (Supplementary Fig. 1). D-dimer (0.14mg/L, Reference range 0–0.50mg/L), Tests were negative for coronavirus disease 2019. The Cardiac Color Doppler Ultrasound, Coronary CTA and chest CT were completed in 24h. Dynamic electrocardiogram (ECG) revealed a normal sinus rhythm without any ST-segment changes. There was no obvious abnormality in the Coronary Artery CTA and chest CT showed no pulmonary infection or congestion. Cardiac Color

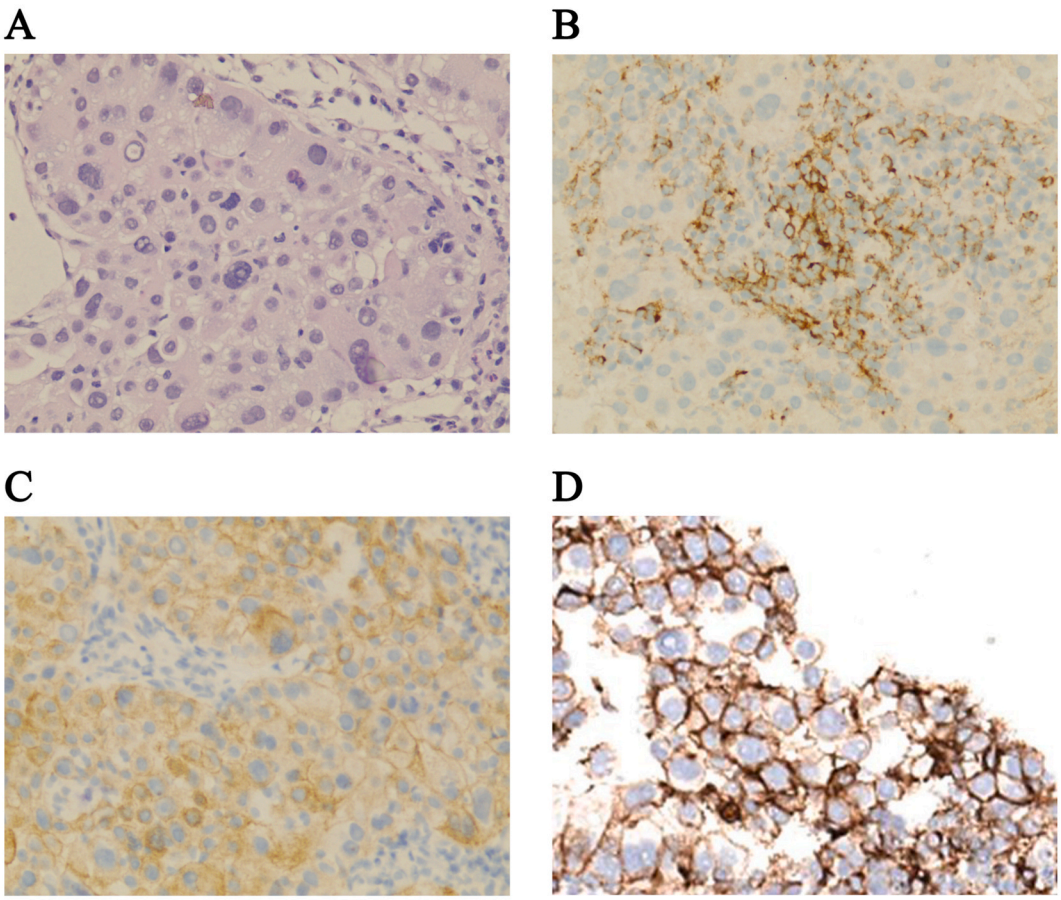

Fig. 1. Histological analysis of LCNEC biopsy. (A) The tumor infiltrated in the shape of a nest, with abundant cytoplasm, unequal and irregular nuclei, unclear nucleoli and visible mitosis. (B&C) Immunohistochemical staining showed the tumor cells were positive for neuroendocrine marker CD56 and synaptophysin. (D) The TPS of PD-L1 was 80%.

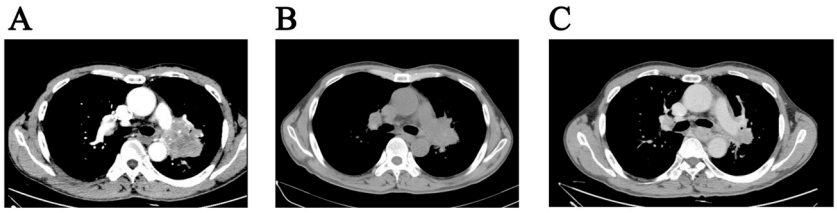

Fig. 2. Changes in tumor volume. (A) 63 mm × 62 mm on February 12, 2020. (B) 43 mm × 29 mm on July 20, 2020. (C) 29 mm × 27 mm on September 8, 2020.

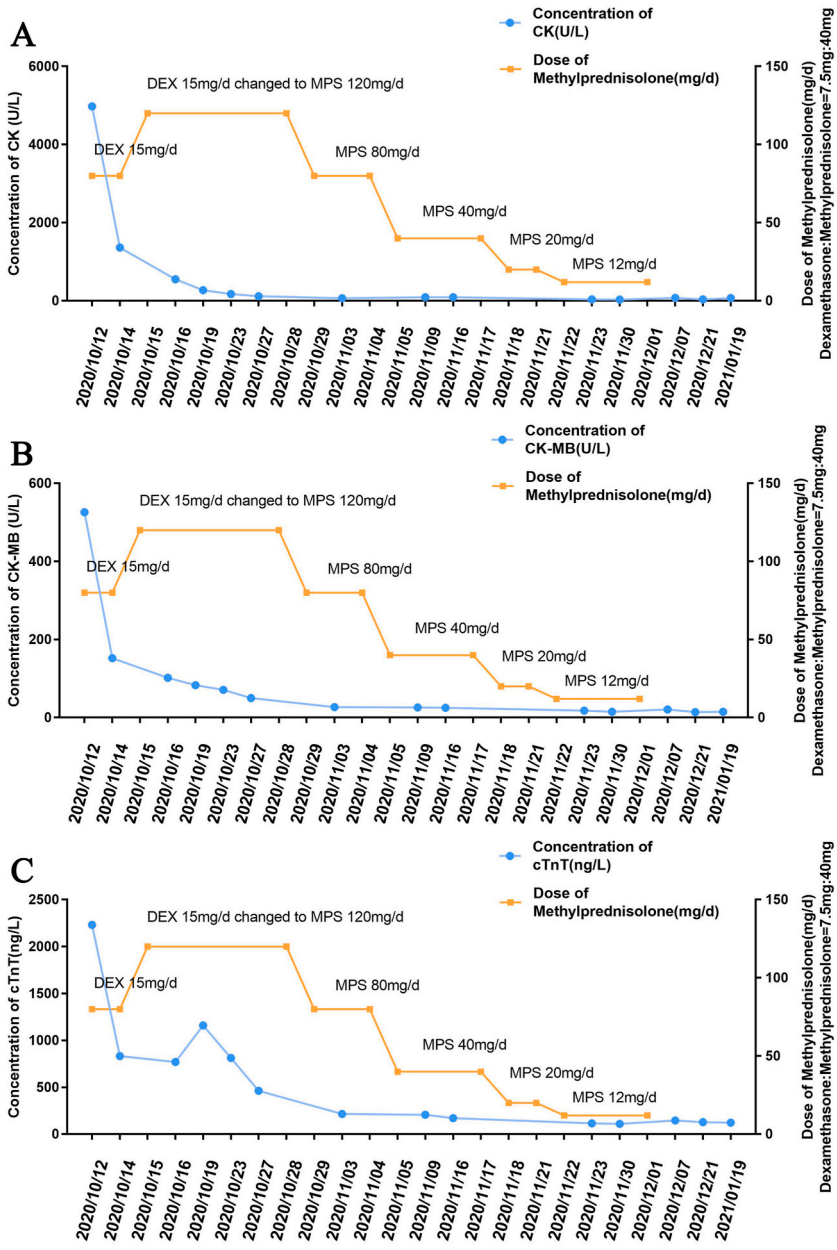

Fig. 3. Changes in biochemical markers. Levels of CK (A), CK-MB (B) and Troponin T (C) after methylprednisolone treatment.

Ultrasound showed enlarge of aorta, normal left ventricular systolic function and poor diastolic function, and a small amount of pericardial effusion. Given that the patient had no special medical history, no symptoms of chest tightness or pain but had been treated with immunotherapy, the diagnosis was considered as "drug-induced myocarditis". The patient was monitored for electrocardiogram, blood pressure, and blood oxygen, as well as control his intake and output. The patient was immediately given dexamethasone 15 mg/day, at the same time, aspirin 0.1g/qd for antiplatelet therapy, atorvastatin 20mg/qd for blood lipid regulation, and Valoxonil 35mg/bid for nutritional myocardial therapy were given, myocardial protective drugs, and the shortness of breath was slightly relieved after 24 h. The CMR suggested a mild decline in cardiac function with myocardial edema in signal-enhanced T2-weighted imaging and in late gadolinium-enhanced (LGE) T1-weighted imaging, as well as pericardial effusion (as shown in Fig. 4, the T2 value of interventricular septum increased to 65.5 ms while the T1 value of interventricular septum was prolonged to 1297.2 ms. The ECV was 37%), left ventricular ejection fraction (LVEF) of 64%, stroke volume of 52 mL, cardiac output of 4.6 L/min and CI of 2.9 L/min/m2. After excluding immune pneumonia and acute coronary events, the patient was diagnosed with Sintilimab-induced myocarditis, according to the abnormal serum myocardial enzyme spectrum with a normal coronary angiograph, myocardial edema, and pericardial effusion in CMR scans, and a correlation between the use of Sintilimab and the onset of clinical symptoms. We then replaced 15 mg dexamethasone with 120 mg methylprednisolone. After continuing treatment for 1 week, the patient's shortness of breath was alleviated, but his activity tolerance was still poor. Although the level of CK and CK-MB continued to decrease (Fig. 3B), cTnT and the NT-ProBNP increased (Fig. 3C, Supplementary Fig. 1), and Cardiac Color Doppler Ultrasound showed that the stroke volume 38 mL. After strengthening diuresis and controlling fluid intake, the shortness of breath was relieved. The cTnT showed a continuous decrease as well (Fig. 3C). Although NT-proBNP increased at the beginning of treatment, it gradually decreased in the later period with continuous

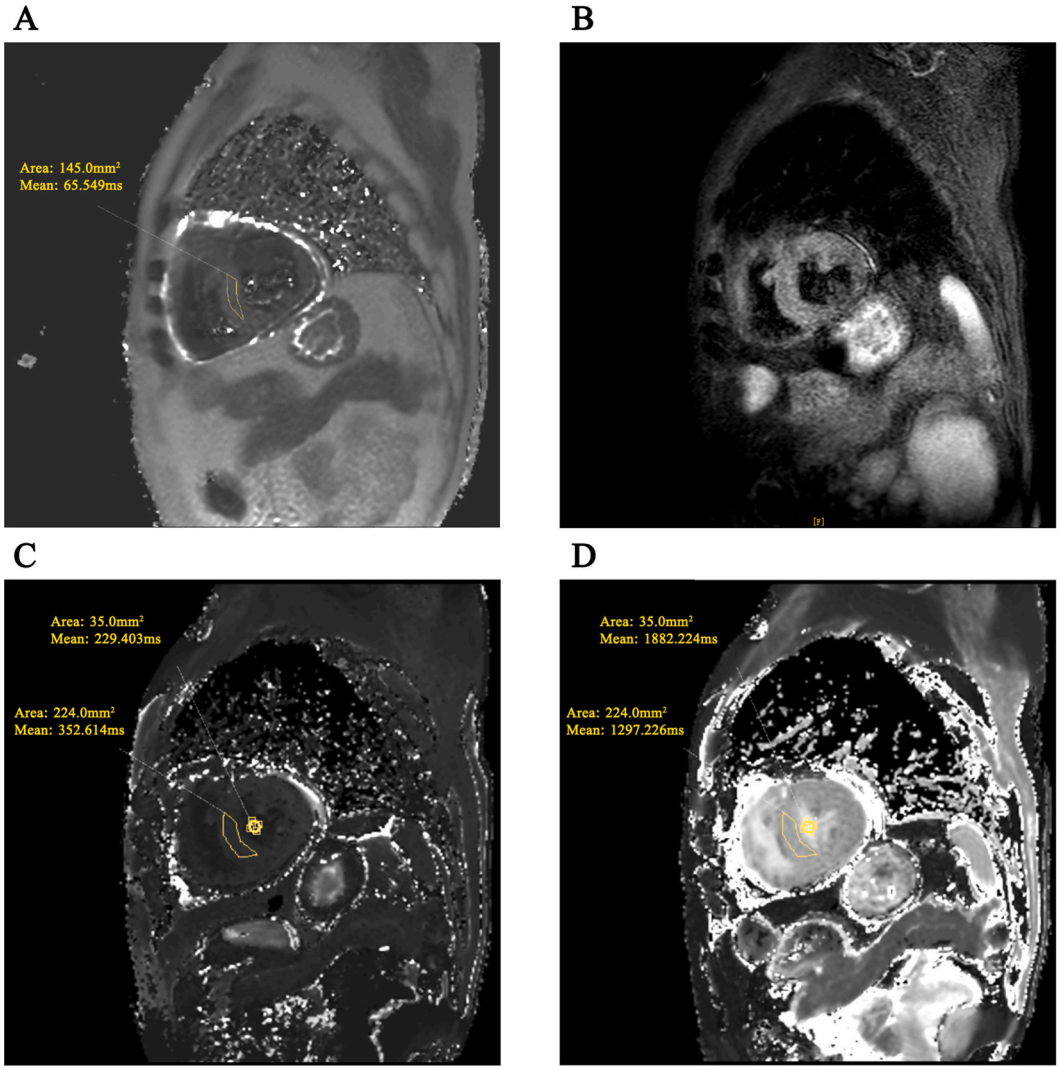

Fig. 4. The images of CMR. (A) T2 value of interventricular septum was 65.549 ms. (B) The signal of myocardium on T2-STIR. (C&D) T1 value of interventricular septum was prolonged to 1297.226 ms, and the ECV was 37%.

use of hormone (Supplementary Fig. 1). After 6 weeks, the CMR revealed that cardiac function had recovered (mainly diastolic function), although myocardial edema was still present and the small amount of pericardial effusion was roughly the same as before. Cardiac function was also improved (LVEF 65%, stroke volume 68 mL, cardiac output 6.7 L/min and CI 3.9 L/min/m2). The dose of methylprednisolone was gradually reduced and stopped after the cTnT decreased to 124 ng/L 7 weeks later. Thereafter, cTnT remained at 100 ng/L weekly, and returned to normal levels 6 months later. During this period, the patient did not receive any anti-tumor treatment and the CT showed that tumor had progressed from 30mm × 33mm–56mm × 46mm. Because the tumor was BRAF-positive, the patients was recommended to use BRAF inhibitors or oral chemotherapy. But for financial reasons, the patient chosed to take Capecitabine orally rather than BRAF inhibitors. After taking Capecitabine for 4 months, the patient underwent CT scan again to assess the therapeutic effect, which was determined to be stable disease (SD). However, the tumor progressed to 72mm × 42mm by CT scan after 2 months and the patient rejected any chemotherapy or targeted therapy at this time.

2. Discussion

Immunotherapy has changed the pattern of tumor treatment. These agents can inhibit the binding of PD-1 on the surface of T cells to the PD-L1 ligand on the surface of tumor cells, and then reactivate the T cells to kill tumor cells. It was found when the patients with Non-Small-Cell Lung Cancer (NSCLC) were treated with combination of Sintilimab and chemotherapy as the first-line treatment, the progression-free survival of patients was significantly improved [7,8]. Moreover, Sintilimab has been proven to be a promising therapeutic regimen in locally advanced head and neck tumors, esophageal cancer, liver cancer and other solid tumors [4–6]. However, in the experimental group of these studies, nearly 43.2% of patients developed irAEs, mainly skin toxicity, followed by endocrine, gastrointestinal and other adverse reactions [7], but adverse events such as myocarditis were seldomly reported. Immunotherapy-induced myocarditis is rare, and only a few cases have been reported. A patient who was treated with Ipilimumab for chronic myelogenous leukemia developed symptoms such as myalgia and dyspnea, and finally died due to complete atrioventricular block and ventricular escape. Skeletal muscle biopsy revealed that he had inflammatory myositis with $CD3^+$ T cell infiltration [9]. Laubli reported a case of using Pembrolizumab in the treatment of metastatic uveal melanoma. The patient developed immune myocarditis with severe heart failure and a significant decrease in the left ventricular EF. Myocardial biopsy showed lymphocyte infiltration mainly composed of $CD8^+$ T cells [10]. Another patient developed chest pain, dyspnea, and Takotsubo cardiomyopathy after treatment with Ipilimumab. PET-CT showed increased uptake of 18F-fluorodeoxyglucose (18F-FDG) in the apex of the left ventricle, which was believed to be caused by immune myocarditis [11]. In addition, a patient experienced dyspnea, edema of both lower extremities, and significantly reduced cardiac EF after being treated with Nivolumab plus Ipilimumab, which was significantly improved after large doses of corticosteroids. However, the patient finally died after re-use of ICIs [12]. Based on the above reports, many patients with immunosuppressant-related cardiotoxicity appear to have classic symptoms and signs of heart failure. Although endomyocardial biopsy is the gold standard for diagnosis of ICI-associated myocarditis, it is seldomly used due to the invasive and high risk of cardiac perforation. When the diagnosis is still uncertain, or before restarting ICI treatment, endomyocardial biopsy should be considered to confirm or refute the diagnosis [13]. In this case, the patient had clinical symptoms of heart failure, and cardiac biomarkers CK-MB, BNP, and cTnT were abnormally elevated. CMR indicated diffuse myocardial signal enhancement on T2WI, with T2 values greater than 45 ms and T1 values greater than 1250 ms, meeting the diagnostic criteria for CMR myocarditis [14]. In addition, cTnT significantly increased in this case, which is a relatively rare case reported so far. cTnT is a specific and sensitive biomarker of myocardial injury. Increased cTnT was commonly observed in acute coronary syndrome, but the patient had no symptoms of chest pain. Dynamic monitoring of electrocardiogram showed no ST segment changes, and electrocardiogram showed no abnormalities. So, acute coronary syndrome was firstly ruled out; elevated cTnT can also be seen in pulmonary embolism, renal insufficiency, and viral myocarditis. As the patient's dynamic monitoring of blood oxygen was normal, D-dimer was detected within the normal range, and no pulmonary hypertension was found on echocardiography, pulmonary embolism was not considered at the beginning. Renal function was tested with normal creatinine, thus, renal failure was excluded. Since no symptoms of infection such as fever was observed before admission, viral myocarditis was ruled out. The patient had no history of hereditary cardiomyopathy or congenital heart disease. Given that he had no history of heart disease but a history of PD-1 therapy, we strongly suspected that the patient had a "drug-induced myocarditis". The incidence of myocarditis related to anti-PD-1, anti-PD-L1, or anti-CTLA-4 treatment alone is 0.5%, 2.4%, or 3.3% [15]. A single center retrospective analysis in China showed that the incidence of myocarditis was 1.06% when using ICIs alone or in combination with chemotherapy [16]. In this case, for drug-induced myocarditis, although he was combined with docetaxel and other chemotherapy drugs, a number of clinical trials about Docetaxel and Cisplatin in Advanced NSCLC showed that the rate of cardiotoxicity was low [17,18]. A meta-analysis of docetaxel versus docetaxel plus cisplatin in the treatment of advanced NSCLC showed that the major toxic side effects were anemia, nausea vomiting, thrombocytopenia, mucositis and nephrotoxicity, no cardiac toxicity has been reported [19].

Studies have reported that 2 patients (4.3%) developed cardiac toxicity, mainly arrhythmia [20]. High dose corticosteroids were used immediately. The rapid improvement of symptoms and the decrease of serum TNT further confirmed the diagnosis of Sintilimab-induced myocarditis. Current study shows that the combination of two ICIs drugs increases the incidence of myocardial infarction [15]. However, whether chemotherapy combined with immune therapy aggravates immune myocarditis still needs to be further explore.

LCNEC is a rare and highly aggressive disease with an incidence of 3% and a poor prognosis in all stages [21]. At present, there is no optimal therapeutic schedule for LCNEC in the clinical practice. As a third-line treatment, Nivolumab was given to a patient with stage IVB LCNEC when the disease progressed after the first- and second-line of chemotherapy [22]. Although Nivolumab was discontinued after two cycles in this patient due to the development of interstitial pneumonia, the disease did not progress within six months. A

retrospective analysis showed that even advanced LCNEC patients with PD-L1-negative had significantly better prognoses when treated with anti-PD-1 therapy than those without the therapy [23]. In our case, the patient was treated with Sintilimab combined with chemotherapy as the first-line treatment for advanced LCNEC due to the high expression of PD-1. The patient achieved partial response, which was confirmed by chest CT. In addition, cardiac enzymes were detected before each treatment. However, the patient presented with dyspnea symptoms and elevated cTnT after five courses of Sintilimab treatment. The significant increase of cTnT indicates that a large number of myocardial necrosis are necrotic, and the condition may worsen at any time. Early diagnosis and medication are essential. Within 24 hours of admission, the patient excluded ACS and other related diagnoses, suspected ICIS-related myocarditis, and was promptly treated with steroids. Subsequent CMR and the effectiveness of steroid therapy further assisted diagnosis. Although the patient had significant symptom relief, cTnT declined slowly. According to the guidelines, steroids should be reduced every 1–2 weeks after the condition improves, and the reduction process may last for 6–8 weeks, or even longer, until the biomarkers of heart injury return to baseline lines and are discontinued [24,25]. After 7 weeks, cTnT still maintained at 124 ng/L, but the patient's symptoms have been significantly alleviated. Considering that long-term use of steroids can cause acute gastric mucosa lesions, peptic ulcer, secondary bacterial, fungal, pneumocystis pneumonia and other opportunistic infections, we reduced the use of steroids eventually after 7 weeks, and observe that the patient's symptoms did not worsen again and cTnT increased. Failure to use high-dose corticosteroids therapy at the initial stage of treatment may result in slow improvement of the condition.

At present, the exact pathogenesis of cardiotoxicity in patients treated with ICIs is still unclear. $CD8^+$ T cells are known to induce cardiac myocyte death and myocardial inflammation. T cell response could be inhibited by SHP-2, a ubiquitously expressed tyrosine-specifific protein phosphatase, which is recruited by PD-1 through binding to PD-L1 or PD-L2 receptor [26,27]. In various mouse models, anti-PD-1 antibody has obvious anti-inflammatory and anti-atherosclerotic effects, and plays an important role in protecting heart tissue from T cell-mediated inflammatory damage. In PD-1 deficient mice, $CD4^+$/$CD8^+$ T cells and macrophages were significantly increased in myocarditis [27,28]. In some cases, endometrial biopsy or skeletal muscle biopsy has shown that T-cell-based lymphocytes and macrophages are the main infiltrates. The genes of infiltrating T cells in the myocardium and those of tumor-reactive T cells in the tumor have been shown to be homologous [9,10,29,30].

In summary, our case herein suggests that increasing clinical surveillance, early diagnosis of immunotherapy-induced myocarditis and timely corticosteroid treatment is essential to reduce the risk of death. Sintilimab has been approved for first-line treatment of advanced NSCLC in China and will be applied to the treatment of more other malignant tumors, it is very important to improve doctors awareness of myocarditis as a potential side effect of ICIs. More reports are required to provide treatment experience.

Author contributions

All authors listed have significantly contributed to the investigation, development and writing of this article.

3. Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16874.

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