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CASE REPORT

Initial Elevated Myocardial Enzymes were Neglected in Lung Adenocarcinoma ICIS Associated Myocarditis: a Case Report

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SUMMARY

Background: **In recent years, immunotherapy has gradually become the first or second-line drug for non-small cell lung cancer. However, the side effects associated with immunotherapy should not be underestimated. Toxic reactions are commonly seen in the skin, endocrine, and liver, and rarely in the heart and nerves. These effects are often life-threatening when they occur. In this paper, we present a case of ICIs-associated myocarditis in advanced lung adenocarcinoma with unappreciated initial cardiac enzyme elevation in a driver gene negative.**
Methods: **After electronic bronchoscopy and pathological examination, the patient was diagnosed with driver gene-negative advanced lung adenocarcinoma and treated with ICIs.**
Results: **Driver gene-negative advanced lung adenocarcinoma, effectively treated with ICIs, initially had elevated cardiac enzymes and unilateral ptosis, but was not taken seriously and the patient eventually died after discharge from the hospital.**
Conclusions: **For patients with driver gene-negative advanced lung adenocarcinoma treated with ICIs, regular and periodic monitoring of myocardial damage markers is a top priority, followed by timely initiation of hormonal therapy as a means to improve prognosis.**
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KEYWORDS

immunotherapy, lung adenocarcinoma, heart muscle damage, driver gene

CASE REPORT

Lung cancer is the leading cause of cancer death worldwide, with an overall 5-year survival rate of 10 - 15% [1]. The annual number of new lung cancer cases in China is about 787,000, of which non-small cell lung cancer accounts for 85%, and about 57% of patients are diagnosed only at stage IV [2]. Due to the development of genetic testing technology, immunotherapy is gradually becoming a first- or second-line agent for non-small cell lung cancer [3]. The benefits of immunotherapy have been accompanied by an increase in side effects associated with ICIs. In this article, we present a case of myocarditis in a driver gene-negative advanced lung adenocarcinoma with ICIs in which the initial cardiac en-

zyme elevation was not taken seriously [4,5].

A 72-year-old female presented with persistent cough and sputum with right-sided chest pain and a history of hypertension and hyperthyroidism. The histopathological findings were adenocarcinoma (alveolar type 100%, moderately differentiated), with genetic testing suggesting TPS 50% - 60%, PD-L1 positivity, and second-generation gene sequencing suggesting KRAS driver mutation (Figure 1 - 2). The patient was finally diagnosed with stage IVB right lung adenocarcinoma with a PS score of 1. Immunotherapy combined with single-agent chemotherapy (specific regimen: carrilizumab 200 mg, pemetrexed 500 mg) was started every 3 weeks for 6 cycles. After 2 cycles of treatment, a repeat chest CT showed a decrease in soft tissue density foci in the lower lobe of the right lung compared with the previous one (Figure 3 - 4).

The patient presented with elevated cardiac enzymes on the eve of cycle 3, along with right-sided ptosis, but this status was not taken seriously. As the patient developed symptoms such as malaise, ICIs myocarditis was considered, glucocorticoid therapy was initiated at the first opportunity, and changes in markers of myocardial injury were monitored (Figure 5). Initially, the patient had myoglobin 166 µg/L (10 - 46 µg/L), high-sensitivity troponin I 199.3 ng/L (0 - 19 ng/L), B-type natriuretic peptide 1,278.2 pg/mL (< 900 pg/mL), and after 72 hours of intravenous treatment with methylprednisolone sodium succinate 40 mg, the patient's symptoms such as right upper eyelid drooping and peripheral weakness was relieved. However, after 72 hours of treatment with methylprednisolone sodium succinate, the patient's symptoms such as right upper eyelid drooping and circumferential weakness were relieved, but the patient's indexes such as myocardial injury markers showed a tendency to increase. After 1 week of glucocorticosteroid treatment, the patient's right upper eyelid drooping and peripheral weakness improved, and the rest of the indexes returned to normal with high-sensitivity troponin 54.9 ng/L (0 - 19 ng/L) and B-type natriuretic peptide 1,044.6 pg/mL (< 900 pg/mL). The patient improved and was discharged from the hospital and transitioned to oral hormone therapy, unfortunately, the patient died 1 month later.

DISCUSSION

In recent years, the use of immunotherapeutic agents in the treatment of non-small cell lung cancer has advanced the current treatment landscape [6-8]. Several therapeutic studies have now shown that immunotherapy combined with chemotherapy is more beneficial in the treatment of patients with advanced lung cancer than immunotherapy alone and chemotherapy alone. Even though the incidence of adverse effects related to immunotherapy combined with chemotherapy is correspondingly higher, these effects are mostly manageable. At the same time, given that immunotherapy combined with chemotherapy is currently considered the first-line treatment option for advanced lung adenocarcinoma [9], we ultimately chose immunotherapy combined with single-agent pemetrexed as the chemotherapy regimen for this patient, and the patient attained good clinical benefit for the completed treatment phase.

With the increasing understanding of immunotherapy, more and more immunotherapy-related toxic reactions are being identified. Immunotherapy-related toxic reactions are most commonly seen in the skin, endocrine, liver, and other organs, while a very small number of patients undergoing immunotherapy acquire immunotherapy-related myocardial damage. Although the incidence of immunotherapy-related myocardial damage is approximately 1.05%, the precise incidence may be underestimated due to the non-specific systemic presentation and the lack of specific markers of myocardial damage [10]. Therefore, it is not easily detectable in clinical work and the high mortality rate makes clinicians susceptible to misdiagnosis, thus demanding a high degree of vigilance for the occurrence of such low incidence but highly harmful toxic reactions during immunotherapy.

Immunotherapy-associated toxic reactions are often seen in the early treatment phase, mostly after 1 - 2 cycles of treatment [11]. Immunotherapy-associated myocardial damage is often presented as chest pain, exertional dyspnea, and, seldom, unilateral ptosis as the first symptom. In this case, the patient first presented with symptoms of right-sided ptosis in the second cycle of immunotherapy, but because it was not taken seriously, peripheral weakness, palpitations, and chest tightness soon developed. Although the first comprehensive tests such as electrocardiogram and cardiac ultrasound were completed, none of them indicated the presence of myocardial damage. It was not until markers of myocardial damage such as troponin and B-type natriuretic peptide suggested abnormalities, thus clarifying that the patient had grade 3 immunotherapy-related side effects with multisystem involvement, that we adjusted the glucocorticoid dosage according to CSCO guidelines. In combination with our patient's recent age and poor cardiovascular condition, the symptoms of unilateral ptosis are often overlooked for these reasons. The lack of specificity in the presentation of myocardial damage related to immunotherapy does not easily gain the attention of clinicians. Therefore, it is particularly important for patients receiving immunotherapy to be regularly watched for biomarkers of myocardial damage such as troponin and creatine kinase, B-type natriuretic peptide, D-dimer, inflammatory markers, electrocardiogram, echocardiogram, and, if necessary, complete cardiac nuclear magnetic examinations. Although myocardial biopsy is the gold standard for confirming immunotherapy-related myocardial damage [12], few patients undergo this test in therapy work.

In summary, for immunotherapy-associated myocardial damage, although the incidence is extremely low, the risk of death is high and early detection and diagnosis is

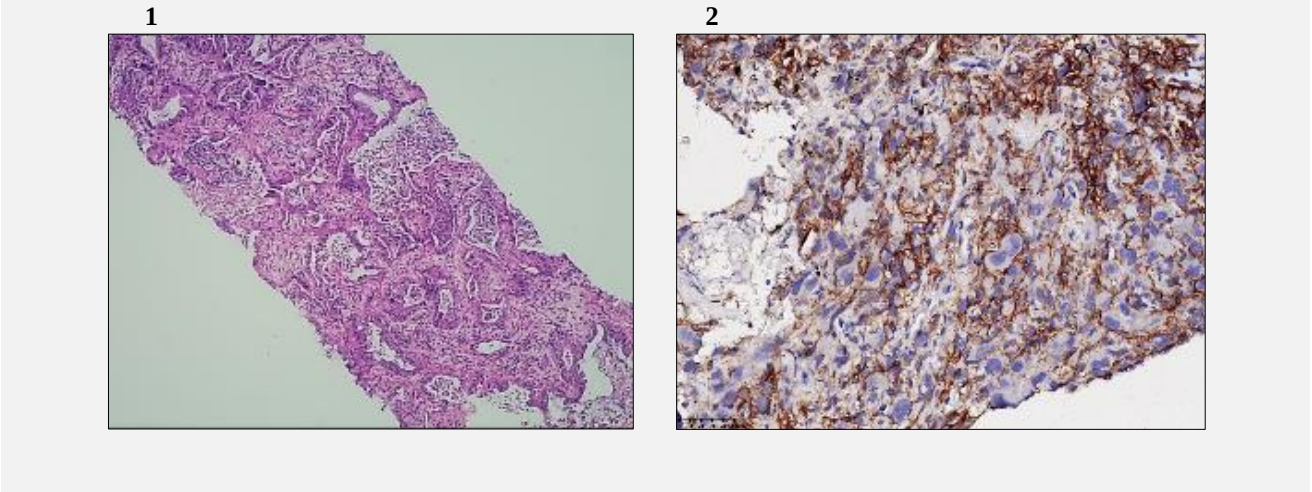

Figure 1, 2. Histopathology suggesting adenocarcinoma (alveolar type 100%, moderately differentiated) with 90% tumor cell content and 1% tissue necrosis ratio.

Immunohistochemistry suggested TPS 50% - 60%, PD-L1 positive, and second-generation gene sequencing suggested KRAS driver mutation.

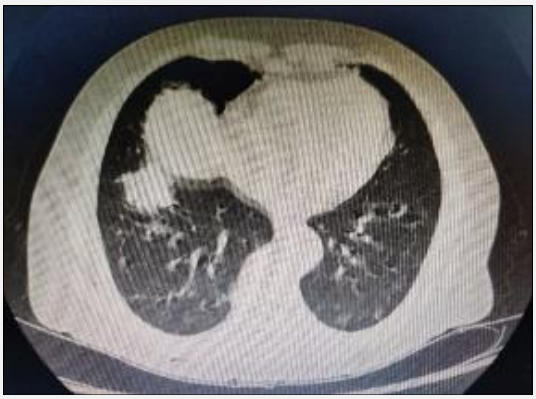

Figure 3. A soft tissue density focus in the right lower lobe of the chest was seen at the time of admission, with less smooth margins, size about 3.0 x 2.2 x 2.0 cm, CT value about 45.0 HU.

the primary measure to avoid eventual exacerbation of immunotherapy-associated toxic reactions. In the case of immunotherapy-associated myocardial damage, it is easy to overlook in the early stages, especially in elderly patients, which can lead to irreversible outcomes. In this case, regular monitoring of markers of myocardial damage, ECG, and, if necessary, cardiac MRI is necessary for immunotherapy-related myocardial damage.

CONCLUSION

For patients with driver gene-negative advanced lung adenocarcinoma treated with ICIs, regular and periodic monitoring of myocardial damage markers is a top priority, followed by timely initiation of hormonal therapy as a means to improve prognosis.

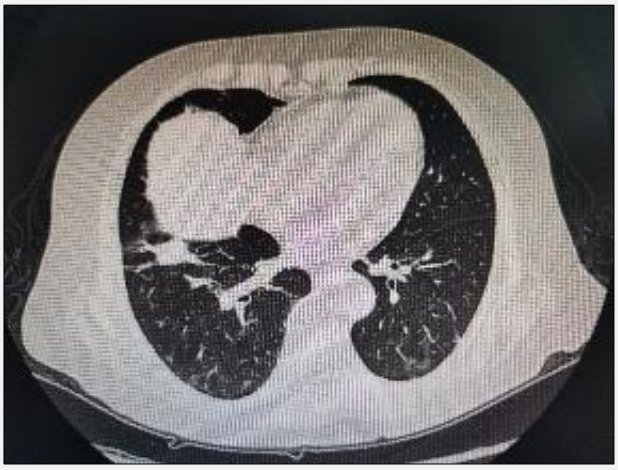

Figure 4. The soft tissue density focus in the right lower lobe of the chest decreased after 2 cycles of immunotherapy combined with single-agent chemotherapy (specific regimen: carrilizumab 200 mg, pemetrexed 500 mg), with less smooth margins, size about 2.3 x 1.3 x 2.0 cm, CT value about 45.0 HU. 2.3 x 1.3 x 2.0 cm, CT value about 45.0 HU.

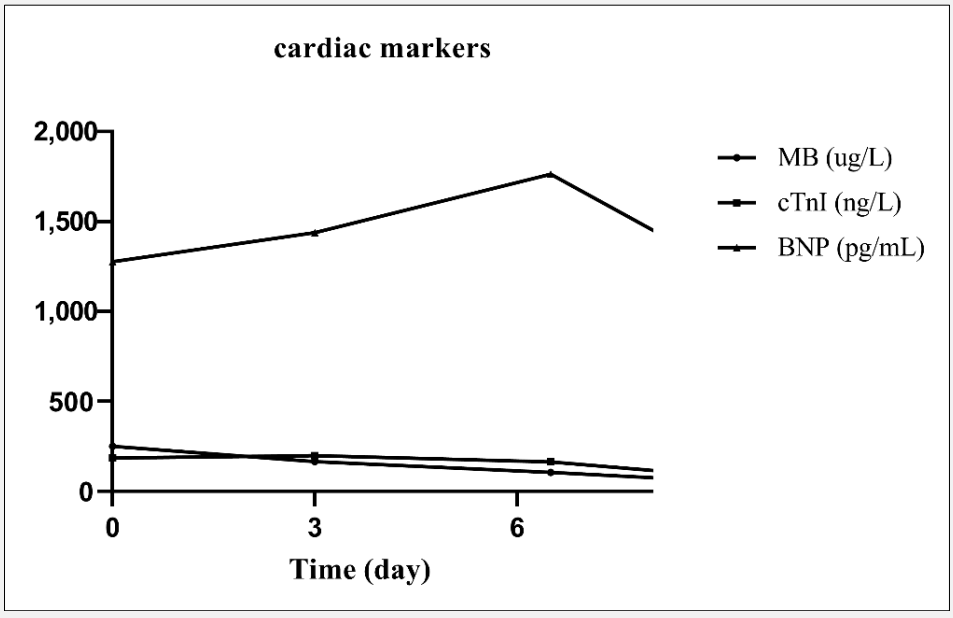

Figure 5. Myocardial injury markers gradually increased in the first 3 days of admission, glucocorticoid therapy was initiated on day 3.

Methylprednisolone sodium succinate 40 mg IV treatment relieved symptoms after 72 hours, but the patient's myocardial injury markers and other indicators tended to increase. Myocardial injury markers gradually decreased after adjusting methylprednisolone sodium succinate 80 mg IV treatment.

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Ethical Approval:
This study was approved by the ethics committee of North China University of Science and Technology Affiliated Hospital. All procedures performed in studies were in accordance with the ethical standards. Informed consent was obtained.

Declaration of Interest:
No conflicts of interest.

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