

## CASE REPORT

# Severe immune-related hyperthermia followed by immune-related pneumonitis with PD-1 inhibitor (sintilimab) in small cell lung cancer: A case report

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## Abstract

Immune checkpoint inhibitors (ICIs) have achieved prominent efficacy in the treatment of numerous cancers, which is the most significant breakthrough in cancer therapy in recent years. However, ICIs are associated with a series of immune-related adverse events (irAEs). Pneumonitis is an uncommon but potentially fatal irAE. In the case reported here, a patient with advanced small cell lung cancer (SCLC) had rapid progression of disease following chemotherapy and received ICIs. The patient experienced severe immune-related hyperthermia followed by immune-related pneumonitis. Fortunately, a good clinical response was achieved after the patient received corticosteroids and tocilizumab.

## KEYWORDS

small cell lung cancer, immune checkpoint inhibitors, sintilimab, hyperthermia, immune-related pneumonitis

## INTRODUCTION

Immune checkpoint inhibitors (ICIs) have been reported to achieve prolonged remission in some patients with refractory tumors and have changed the treatment landscape in a variety of cancers including small cell lung cancer (SCLC).<sup>1</sup> Sintilimab is a selective antiprogrammed cell death-1 (PD-1) antibody proven to be effective in non-small cell lung cancer (NSCLC).<sup>2</sup> Although ICIs are generally better tolerated than chemotherapy drugs, severe and rare adverse events can occur, especially if they are not recognized and treated promptly.<sup>3</sup> Pneumonitis is an uncommon but potentially fatal toxicity of all reported irAEs. A meta analysis showed the overall incidence of pneumonitis during PD-1 inhibitor monotherapy was 2.7% (95% CI, 1.9%–3.6%) for all-grade and 0.8% (95% CI, 0.4%–1.2%) for grade 3 or higher pneumonitis.<sup>4</sup> Pneumonitis also appears to be less commonly reported with anti-CTLA-4 treatment than with anti-PD-1/PD-L1 treatment.<sup>5,6</sup>

## CASE REPORT

On March 6, 2020, a 35-year-old man was admitted to our hospital with a right supraclavicular mass, which had progressively enlarged for one month together with a history of swelling of the face and neck for a week. His performance status (PS) score was 1. The patient had smoked for more than 20 years and was in good health without any other evidence of disease. PD-L1 expression was unknown. A computed tomography (CT) scan of his neck revealed multiple enlarged lymph nodes bilaterally in the supraclavicular fossa region, multiple small bilateral lymph nodes deep in the cervical region, and space-occupying lesions in the right upper mediastinum (Figure 1(a)). Ultrasound-guided puncture biopsy of the right supraclavicular mass revealed enlarged right supraclavicular lymph nodes, indicative of metastatic SCLC. According to the combined Veterans Administration Lung Study Group/AJCC TNM staging system, the patient was diagnosed with right SCLC T<sub>3</sub>N<sub>3</sub>M<sub>0</sub> stage IIIC with

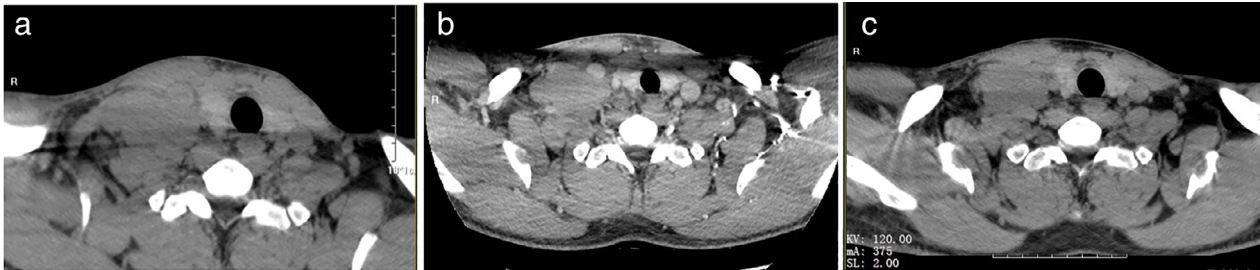
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bilateral supraclavicular lymph node metastasis, and superior vena cava syndrome. The patient received two cycles of chemotherapy, including one cycle of chemotherapy: etoposide 1.7 g D1-D3, lobaplatin 50 mg D1 in March and one cycle of chemotherapy: irinotecan 110 mg D1 and D8, lobaplatin 50 mg D1, apatinib (orally) 250 mg D1-D28 in April (Figure 1(b), 2(a), Figure 1(c), 2(b)). He was

determined to have progressive disease (PD). A superior vena cava balloon dilatation stent implantation was performed in April following which the patient's postoperative facial and neck swelling was significantly relieved.

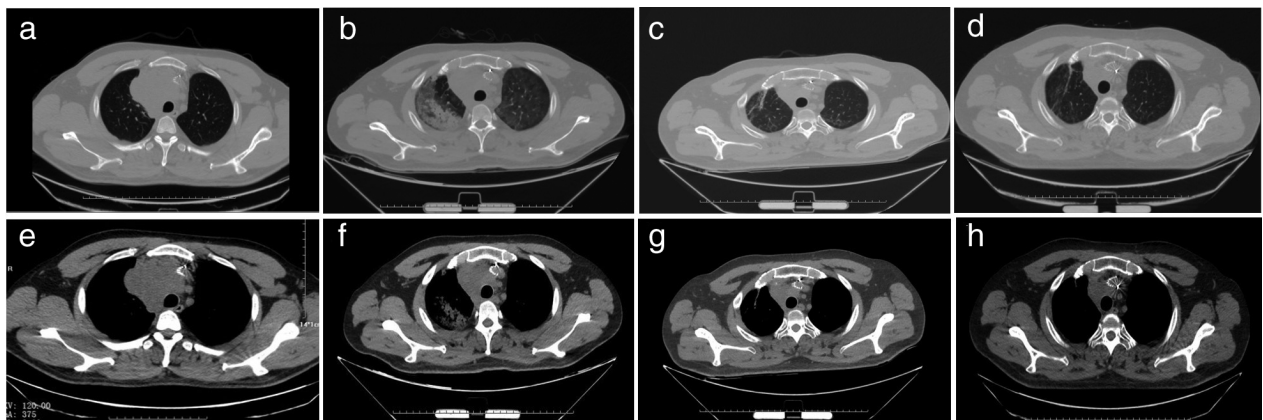
In May, the patient received docetaxel 120 mg D1, gemcitabine 1.6 g D1 and D8, sintilimab 200 mg D1, anlotinib (orally) 12 mg. That night, the patient experienced chills and



**FIGURE 1** Computed tomography (CT) images of the neck at different stages. (a) CT scan at baseline. (b) CT scan after one cycle of chemotherapy with etoposide and lobaplatin. (c) CT scan after one cycle of chemotherapy with irinotecan, lobaplatin and apatinib



**FIGURE 2** Computed tomography (CT) images of the chest at different stages. (a) CT scan after one cycle of chemotherapy with etoposide and lobaplatin. (b) CT scan after one cycle of chemotherapy with irinotecan, lobaplatin and apatinib



**FIGURE 3** Computed tomography (CT) images of the chest after administration of sintilimab. (a, e) Chest CT scan during immune-related hyperthermia. (b, f) Chest CT scan indicated new confluent ground-glass (GG) and reticular opacities in bilateral lungs, suggestive of immune-related pneumonitis. (c, g) After treatment with steroids, the patient's symptoms significantly improved. (d, h) Chest CT scan revealed the mediastinal lesion and multiple enlarged lymph nodes were stable and the pleural effusion had disappeared

hyperthermia, and his temperature reached 39.0°C. Blood routine examination confirmed normal white blood cell, neutrophil and monocyte counts. A chest CT showed that the lesions were stable (Figure 3(a), (e)). The patient received oral prednisone 30 mg for three days, and then received intravenous methylprednisolone 120 mg instead of prednisone. The results of his cytokine profile showed that the levels of interleukin-6 (IL-6) had increased (Table 1). He subsequently received tocilizumab 240 mg twice in order to reduce any adverse reactions. The patient's temperature had been lower than 38°C since June. The methylprednisolone dose was gradually tapered to 60 mg in a week, and replaced by prednisone 50 mg. Prednisone was tapered to 45 mg in a week and thereafter. In June 2020, the patient underwent supraclavicular and mediastinal lymph node radiotherapy (planning target volume [PTV]: 6000 cGy/200 cGy/30f, PTV1: 6000 cGy/200 cGy/30f, Figure S1). The patient ceased taking prednisone of his own accord after feeling better. However, in July 2020, he experienced wheezing and coughing. A chest CT scan showed new confluent ground-glass and reticular opacities in bilateral lungs (Figure 3(b), (f)). Intravenous methylprednisolone 120 mg was recommenced. Fungal smears, sputum culture and bronchoalveolar lavage fluid did not reveal any causative microbial organism, and he was thought to have developed immune-related pneumonitis. After 18 days, the patient's symptoms were relieved. A chest CT re-examination showed significantly improved confluent ground-glass and reticular opacities in bilateral lungs (Figure 3(c), (g)). Methylprednisolone dose was gradually tapered to 60 mg in a week and replaced by prednisone 50 mg. Prednisone was tapered to 45 mg

in a week and thereafter. A CT scan of the patient's chest in August 2020 revealed a therapeutic effect of partial remission had been achieved (Figure 3(d), (h)).

## DISCUSSION

SCLC carries a high tumor mutation burden and lacks functional P53 and Rb1, suggesting that it is sensitive to immunotherapy.<sup>7,8</sup> Meanwhile, the recent results from immunotherapy trials are encouraging.<sup>9–12</sup> However, a series of irAEs, as the consequence of off-target immune attack on the hosts' healthy tissues, have been reported. IrAEs can occur at any time, including after discontinuation of ICIs.<sup>3</sup> irAEs may also be associated with clinical response to therapy.<sup>5</sup> The occurrence of irAEs may be considered a surrogate of clinical activity and improved outcomes.<sup>13</sup> Pneumonitis is a relatively uncommon but potentially fatal and serious irAE. The main symptoms of pneumonitis are cough, dyspnea, fever and chest pain.<sup>14,15</sup> Pneumonitis is typically a diagnosis of exclusion. Chest CT scan is crucial for confirming pneumonitis and evaluating its cause. Bronchoalveolar lavage fluid contains high levels of T cell immunoglobulin, which also indicates immune-related pneumonitis.<sup>16</sup> In the setting of sintilimab therapy and radiotherapy, it is not easy to distinguish radiation pneumonitis (RP) from immune pneumonitis. RP typically develops 4–12 weeks following completion of radiotherapy and may be followed by radiation fibrosis within six to 12 months of completing treatment in a subset of patients.<sup>17</sup> RP is usually limited to the portion of the lung that has been within the radiation treatment portals, and it appears radiologically as ground-glass opacities, nodular and focal consolidation, or both.<sup>17</sup> When pneumonitis is suspected, timely use of corticosteroids are essential.<sup>18</sup>

Sintilimab is a fully human IgG4 monoclonal antibody that binds to PD-1, thereby blocking the interaction of PD-1 with PD-L1 and PD-L2.<sup>19</sup> Compared with other PD-1 inhibitors (pembrolizumab or nivolumab), sintilimab has a different binding site and potentially greater affinity against PD-1 according to preclinical data.<sup>20</sup> There have been several studies where sintilimab has been used in the treatment of various solid tumors, including NSCLC.<sup>19</sup> In ORIENT-11, the median PFS was significantly longer in the sintilimab-combination group than that in the placebo-combination group (8.9 vs. 5.0 months).<sup>21</sup> In a multicenter, phase Ib trial (NCT02937116), treatment was safe and well tolerated with a satisfying efficacy in patients who received sintilimab.<sup>22</sup> In

TABLE 1 Cytokine profile and reference value results

Cytokines	Value at presentation	Reference
IL-6	15.25 pg/ml	≤5.40 pg/ml
IL-1β	27.47 pg/ml	≤12.40 pg/ml
IL-10	15.65 pg/ml	≤12.90 pg/ml
IL-8	22.55 pg/ml	≤20.60 pg/ml
IFN-γ	167.32 pg/ml	≤23.10 pg/ml
IL-5	2.21 pg/ml	≤3.10 pg/ml
IL-12P70	0.83 pg/ml	≤3.40 pg/ml
IL-2	2.48 pg/ml	≤0.75 pg/ml
IL-17	1.16 pg/ml	≤21.40 pg/ml
IL-4	2.00 pg/ml	≤8.56 pg/ml
TNF-α	2.58 pg/ml	≤16.50 pg/ml
IFN-α	0.75 pg/ml	≤8.50 pg/ml

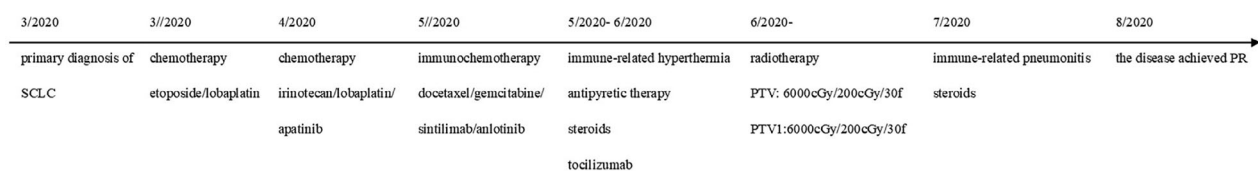


FIGURE 4 Time axis of antitumor treatment and intervention on immune-related hyperthermia and immunerelated pneumonitis

addition, some studies have reported that sintilimab is effective in the treatment of NSCLC.<sup>23,24</sup>

In the case reported here, we present a patient with advanced SCLC whose disease failed and progressed rapidly whilst undergoing chemotherapy. He was then treated with sintilimab and experienced immune-related hyperthermia. Corticosteroids and tocilizumab were used to alleviate the immune response. He ceased to take corticosteroids of his own accord. This was followed by immune-related pneumonitis. Corticosteroids were readministered and a good response was achieved (Figure 4). Although the patient received only one dose of sintilimab, and developed immune-related hyperthermia followed by immune-related pneumonitis, a good clinical effect was obtained.

In conclusion, ICI therapy is a novel strategy for treating patients with numerous cancers including SCLC. However, it is associated with irAEs of which pneumonitis is potentially the most severe and life-threatening. Prompt use of corticosteroids is essential for controlling severe pneumonitis and other irAEs. If the level of inflammatory cytokines increases, the use of biologics targeting inflammatory cytokines can also benefit the patient. IrAEs may also be associated with clinical efficacy.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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