

Occurrence of hyperprogressive disease following administration of immune checkpoint inhibitors in lung squamous cell carcinoma: A case report

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Received April 30, 2022; Accepted July 15, 2022

DOI: 10.3892/etm.2022.11554

Abstract. Immunotherapy through blocking programmed cell death 1, programmed death-ligand 1 and cytotoxic T lymphocyte antigen 4 is developing rapidly and has gained increasing attention as a treatment for malignant tumors. However, some patients experience varying degrees of immune-related side effects after undergoing immunotherapy, with hyperprogressive disease (HPD) occurring in severe cases which increases the risk of mortality. The present study discussed the risk factors for HPD following immunotherapy in a case of lung squamous cell carcinoma, after treatment with a combination of anti-angiogenic drugs and biological cytotoxic drugs, the mass was found to have become smaller than before, along with follow-up treatment options, to provide a reference for clinical treatment decisions.

Introduction

The immune checkpoint is located on the surface of T cells or tumor cells as the target of action to inhibit T cell over-activation. Inhibitory checkpoint protein will prevent T cells from approaching the tumor, weakening the ability of the immune

system to recognize and destroy tumor cells. In addition, the T lymphocyte has become a central focus for engaging the immune system in the fight against cancer, the immunotherapy including checkpoint blockade, adoptive cellular therapy and cancer vaccinology (1). Immunotherapy is treatment that uses the patient's own immune system to fight cancer and can boost or change how the immune system works by regulating the immune microenvironment (2). Therefore, it can find and attack cancer cells at several important nodes. Solid tumors can induce programmed death-ligand 1 (PD-L1) expression, targeting programmed cell death 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) pathways in tumor therapy to avoid the escape from the immune response (3). PD-1 is a key mediator in the induction of T cell exhaustion in chronic inflammation or patients with cancer (4). As an important checkpoint protein that negatively regulates immune responses, PD-1 is expressed on immune cells, especially activated T cells, natural killer cells, B lymphocytes, macrophages and dendritic cells (5,6). PD-L1 can be stimulated by IFN- γ released from activated T cells, PD-1 conformation is induced by the interaction between PD-L1 and PD-1 extracellular structural domains to weaken T cell activation signals, causing them to gradually lose the ability to produce IL-2, TNF- α , IFN- γ and Granzyme B, allowing tumor cells to evade immune attack (7).

However, it can be reversed by blocking the interaction between PD-1 and PD-L1 (8). In recent years, immune checkpoint inhibitors (ICIs) have shown durable remissions and improved long-term survival in a variety of types of cancer (9). For patients with advanced non-small cell lung cancer (NSCLC), the main treatment goal is to prolong survival time and improve quality of life. In NCCN guidelines, platinum-based chemotherapy is used in combination with other cytotoxic drugs, as a conventional treatment option to kill cancer cells by inhibiting cell division (10). With the development of whole gene sequencing in the molecular biology of lung cancer, many targeted drugs are also recommended for first-line treatment in patients with specific patients (11). Following chemotherapy and targeted therapy, tumor immunotherapy through blocking the receptors such as PD-1 and CTLA-4 has become an important treatment option for NSCLC. In the clinic, in addition to the patients with a PD-L1

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Abbreviations: HPD, hyperprogressive disease; PD1, programmed cell death 1; CTLA-4, cytotoxic T lymphocyte antigen 4; TMB, tumor mutational burden; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; TTF, treatment failure time; TV, volume of the primary tumor

Key words: immune checkpoint inhibitors, hyperprogressive disease, lung squamous cell carcinoma, immunotherapy, clinical treatment options

expression level of more than 1%, patients with high tumor mutational burden (TMB), microsatellite instability will also benefit from receiving ICIs (12,13).

However, only 20% of patients with advanced NSCLC respond to immunotherapy and are able to achieve long-term benefits (14). Most other patients who undergo immunotherapy may experience different degrees of immune-related side effects and even accelerated tumor progression, known as hyperprogressive disease (HPD), which affects subsequent immunotherapy and increases the risk of death (15). The HPD reported in a retrospective study was mainly observed in NSCLC, head and neck squamous cell carcinoma, and urothelial carcinoma (16). Regardless of whether chemotherapy or targeted therapy is administered, HPD has been observed in a variety of preclinical/clinical research models. However, the incidence of HPD following immunotherapy is much higher than that after other types of therapies (17,18).

In the present study, the risk factors for development of HPD following immunotherapy and the follow-up treatment options were discussed in light of the treatment process of a patient with lung squamous cell carcinoma, in order to provide some reference for clinical treatment decision-making and the application of ICIs in research.

Case report

On February 23, 2020, a 45-year-old man, with a history (1 month) of dry irritating cough and hemoptysis. The patient had a 15-year history of smoking (6 cigarettes per day), without industrial poison, dust or history of radioactive exposure in the working environment and without family genetic predisposition disease. The patient underwent a chest CT scan: A large soft-tissue density mass was observed in the upper lobe of the right lung, with clear boundaries, ~10.3x7.5 cm in size, uneven density, and violation of chest wall. The patient was diagnosed with lung squamous cell carcinoma based on the pathological biopsy results (TNM stage: T₄N₀M₀; Fig. 1A). The treatment process and changes in the condition of the patient are summarized in Fig. 2. First, genetic testing revealed a mutation in the *EGFR* exon 18 gene, with a mutation rate of 27%. Efficacy of the third-generation TKI treatment after 1 month was evaluated with imaging examination to achieve partial response (Fig. 3). On July 16, 2020, a re-examination of the chest CT revealed that the tumor had progressed and filled the cavity (Fig. 3); consequently, the treatment was switched to targeted therapy and chemotherapy.

Re-examination of the chest CT on October 16, 2020, showed that the tumor was enlarged, with the appearance of multiple small pulmonary nodules and thickened adrenal nodules, in addition, a new metastasis was diagnosed. As the disease progressed, small cell transformation could not be ruled out based on the mechanism of drug resistance. Biopsy revealed squamous cell carcinoma of the lung. Furthermore, immunohistochemistry showed the following results: P63 (+), CK7 (+), TTF-1 (-), CK5/6 (+), Ki67 (+, ~60%), PD-1 (-), and PD-L1 (+, ~40%) (Fig. 1B). In accordance with the indications for immunotherapy, immune checkpoint inhibitors treatment, combined with paclitaxel + Carboplatin regimen, was administered. Then, three days later, the patient developed persistent high fever, the highest temperature reached was 39°C and the

Table I. Time change table of right lung tumor tissue size and the treatment schema.

Date	Treatment schema	Date	Size (cm)
		2020.02.23	10.3x7.5
2020.03.05	GP	2020.03.14	10.8x8.0
2020.04.03	TKI + GP	2020.05.16	3.5x3.5
	TKI	2020.06.26	4.4x2.2
	TKI	2020.07.16	5.1x2.7
2020.07.17	TKI + GP	2020.08.07	5.2x2.8
	TKI + GP	2020.09.18	6.9x4.1
2020.09.26	TKI	2020.10.16	8.9x4.8
2020.10.21	ICIs + TCb	2020.11.03	12.1x6.1
	Stop ICIs	2020.11.13	13x6.8
2020.11.17	TCb	200.11.28	13.2x8.2
		2020.12.13	14x8.9
2020.12.15	NP + anlotinib	2021.01.05	12.3x7.8
2021.01.06	NP + anlotinib	2021.01.26	11.4x7.9

GP, gemcitabine + Cisplatin; TKI, tyrosine kinase inhibitor; ICIs, immune checkpoint inhibitors; TCb, paclitaxel + Carboplatin; NP, vinorelbine + Cisplatin.

chest CT showed inflammatory exudative changes, considering immune pneumonia, stopped immunotherapy, and improved following hormone pulse therapy. Imaging examination of the patient revealed that the diameter of the primary metastatic focus in the lung increased continuously and rapidly, with many new metastatic foci being detected as well. Considering that the patient had HPD, imaging results following treatment with anti-anlotinib, combined with vinorelbine + Cisplatin regimen, for two cycles showed no changes in the primary focus of lung and liver metastases. Hence, the condition was evaluated as stable disease. However, the metastatic foci of the brain and adrenal glands were still in progression. The imaging results of the patient from the time of administration of immunotherapy to January 26, 2021, were summarized as shown in Fig. 4 (imaging results of the primary lung, left lung, adrenal, brain, bone, and liver metastases). Moreover, the size of the primary lung mass during treatment was monitored (Table I). Meanwhile, changes in keratin 19 fragment and hypersensitive C-reactive protein were consistent with the development of the disease (Fig. 5).

Discussion

With the arrival of the new era of immune tumor therapy, the clinical application of immunotherapy is becoming increasingly common. ICIs have greatly influenced the treatment strategy for advanced malignant tumors (19). However, unlike cytotoxic drugs, ICIs may lead to rapid disease progression rather than benefitting the patient during treatment, which in turn may result in reduced survival time and even mortality (20,21). At present, although no unified evaluation criteria for HPD have been published, the immune-related RECIST criteria are recommended to evaluate the efficacy

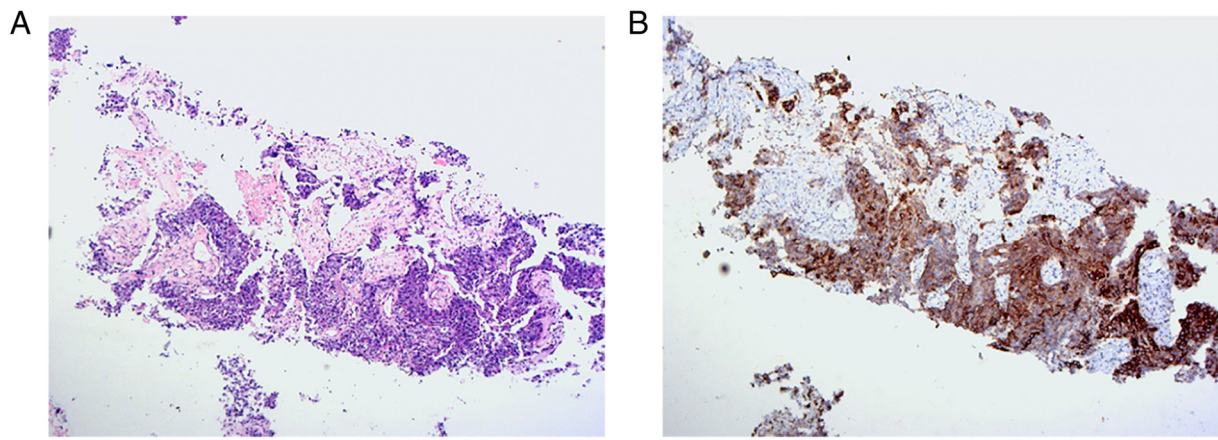


Figure 1. Pathology slides of the biopsy specimen with stains. (A) Hematoxylin and eosin staining and (B) Immunohistochemistry of PD-L1 staining, PD-L1 expression was found to be ~40%. PD-L1, programmed death-ligand 1.

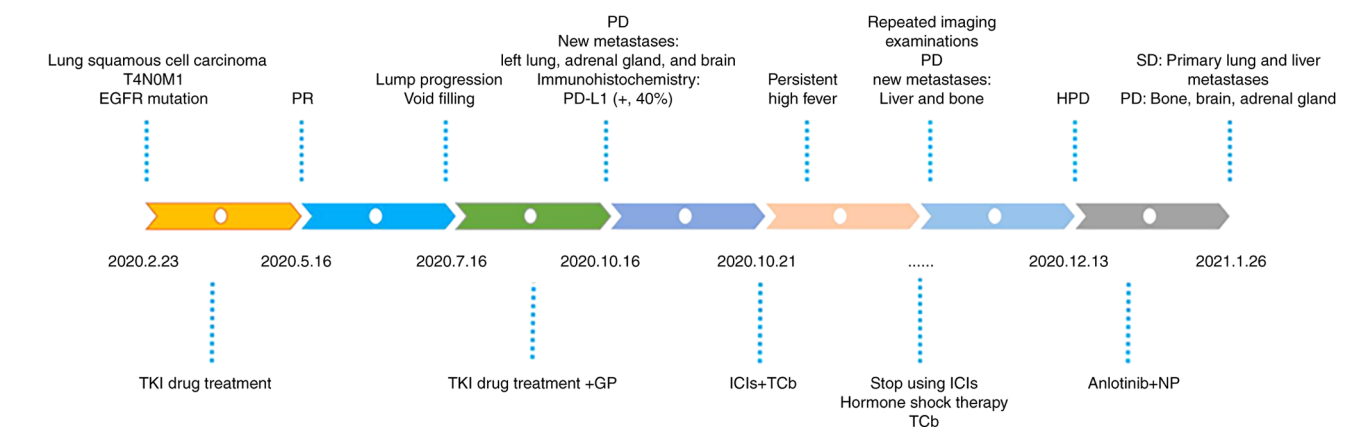


Figure 2. Whole treatment schema and disease change schedule of the patient. TKI, tyrosine kinase inhibitor; GP, gemcitabine + Cisplatin; TCb, paclitaxel + Carboplatin; NP, vinorelbine + Cisplatin.

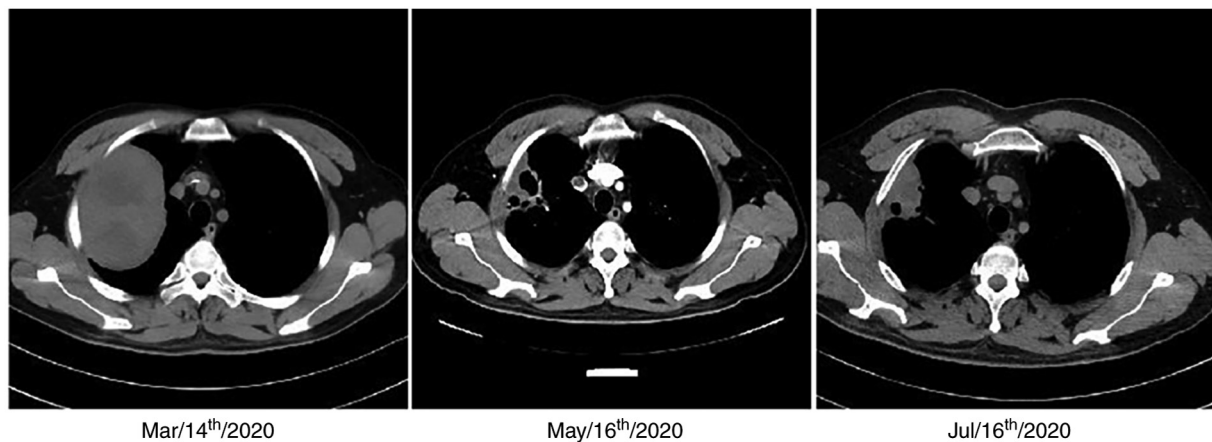


Figure 3. Comparison of imaging results of primary lung lesions before, 1 and 2 months following TKI treatment in patients. TKI, tyrosine kinase inhibitor.

of ICIs (22). Among the various standards describing HPD in available literature, the present study selected the method described by Russo *et al* (23), which is mostly used for patients with NSCLC receiving ICI treatment. The following parameters were considered: i) Treatment failure time (TTF) <2 months (TTF is defined as the time from the start of

ICI treatment to its withdrawal); ii) increase in target lesion volume between the time of the baseline and first radiological assessment $\geq 50\%$; iii) occurrence of at least two new injuries between the time of the baseline and first radiological assessment in organs that are already involved; iv) spread of the disease to a new organ between the time of the baseline and

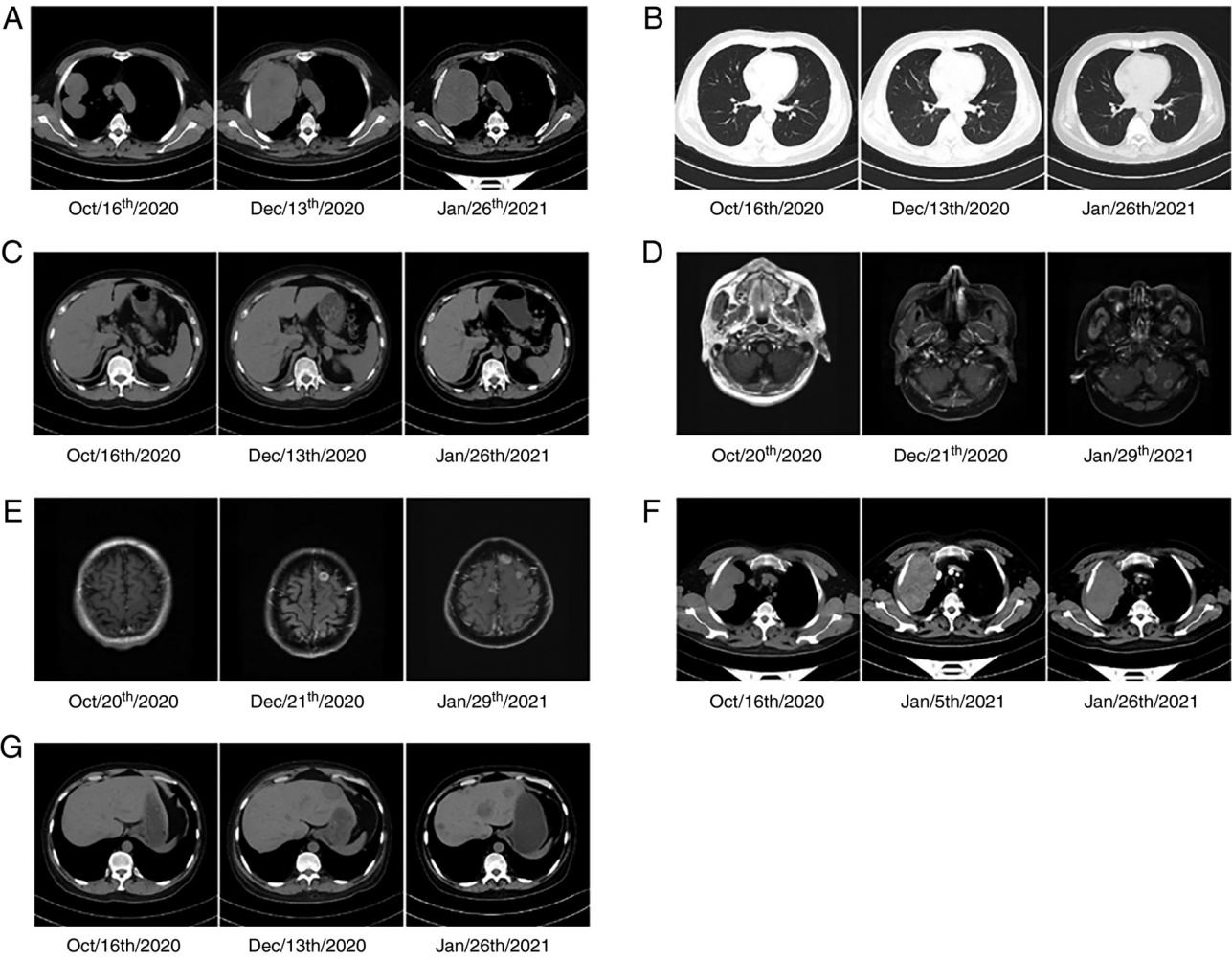


Figure 4. Imaging examination before and after immunotherapy and changes in imaging results following anti-vascular therapy combined with chemotherapy, after the occurrence of HPD. Results of imaging examination of (A) primary lung tumors, and represents the results of imaging examination of the metastatic lesions of (B) left lung, (C) adrenal gland, (D and E) brain, (F) bone, and (G) liver. HPD, hyperprogressive disease.

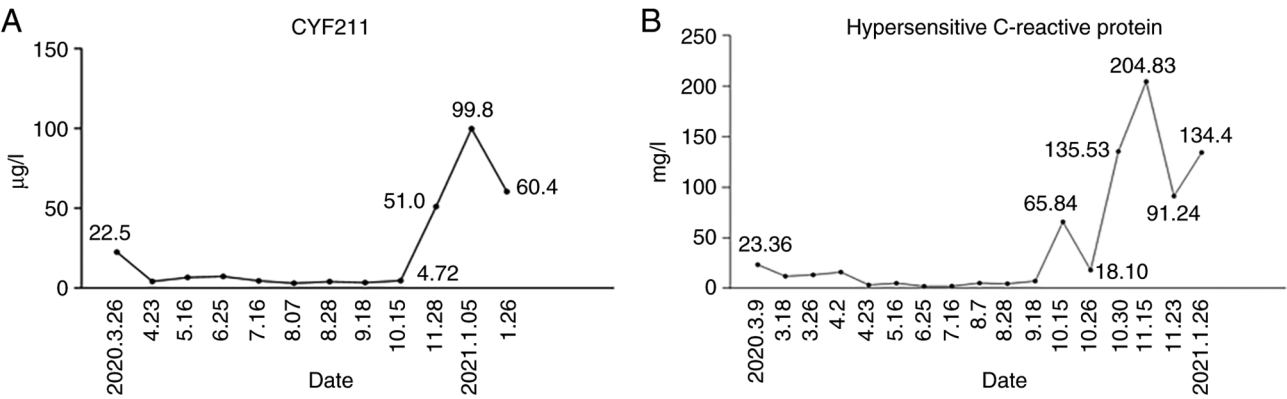


Figure 5. Changes in (A) CYF211 and (B) hypersensitive C-reactive protein expression during treatment. The proteins were found to change along with the progression of the disease, which is consistent with the development of the disease.

first radiological assessment; and v) clinical deterioration with decrease in Eastern Cooperative Oncology Group performance status ≥ 2 during the first 2 months of treatment (24).

The patient developed a persistent high fever after being administered ICIs for the first time. Therefore, the treatment regimen of ICIs was discontinued. Chest CT was reexamined

on December 13, 2020 to evaluate the patient's condition. The method described by Dejacó *et al* (25) was used to calculate volume of the primary tumor (TV) according to the following formula:

$TV = (\overline{xyz}) \times \pi / 6$, where x , y , and z are three vertical tumor diameter measurements in centimeters.

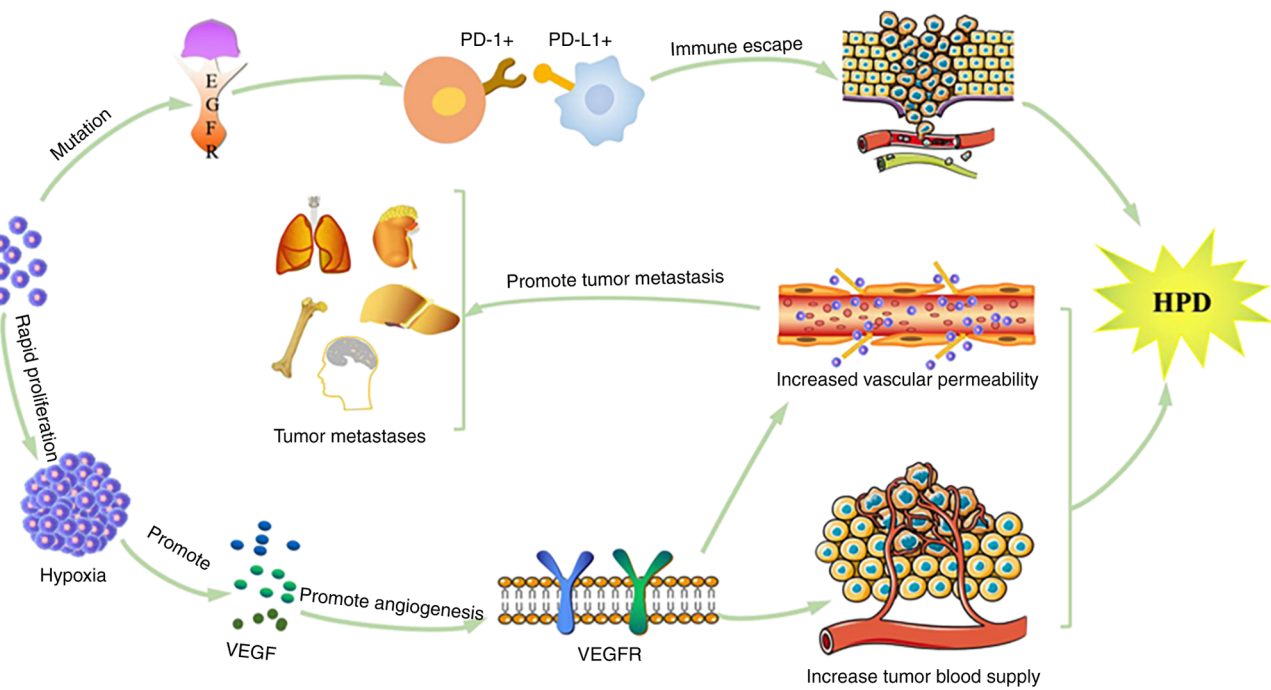


Figure 6. Mechanism of HPD in tumor patients following immunotherapy. HPD, hyperprogressive disease.

According to the calculation, volume of the primary tumor in the right lung of the patient was 4.7 times larger than that observed in the chest CT at baseline (December 13, 2020; shown as Supplementary materials). The metastatic foci of the right lung, brain, and adrenal gland of the patient were found to have increased and enlarged, with new metastases of the liver and bone appearing as well. Following immunotherapy, the patient had a weak physique, spent most of their day lying in bed, could only complete the basic tasks of life and had lost the ability to work. According to the aforementioned RECIST criteria, the patients who meet these conditions are considered to have HPD following ICI treatment. The mechanism of HPD is complex and variable. Although hyperprogression following immunotherapy has been reported in different types of cancer, its mechanism remains to be elucidated. According to related literature reports, patients who have large baseline masses, *EGFR* mutations, inflammatory reactions, and more than or equal to two metastatic lesions at baseline are more likely to develop HPD (26-29). Therefore, the HPD phenomenon observed in this patient was discussed based on the above risk factors, as shown in Fig. 6.

At the beginning of the patient's illness, genetic analysis showed a mutation in exon *EGFR*18, with a mutation rate of 27%. It has been reported that 20% of patients with *EGFR* mutations develop HPD following immunotherapy (30). It is hypothesized that *EGFR* gene mutation upregulates the expression of PD-1, PD-L1, and CTLA-4 by activating downstream signaling pathways, resulting in immune system disorders and ultimately tumor immune escape (31). It has been reported that the discontinuation of previous treatment, especially targeted therapy, or the shift from targeted therapy to immunotherapy may lead to rapid progression of the disease (32). However, the mechanism underlying the enhancement of immune hyperprogression remains to be elucidated. Furthermore, *MDM2/4* may also participate in HPD and may be used as a reference

for screening patients suitable for immunotherapy, to avoid the occurrence of HPD.

Accumulating evidence has shown that the large baseline mass and exponentially growing tumor cells in patients lead to hypoxia in some tumor tissues and high-level secretion of VEGF (33,34). VEGF activates the resting endothelial cells of the surrounding blood vessels and forms immature blood vessels, resulting in increased vascular permeability and leakage, which further promotes tumor growth and metastasis (35). Moreover, the degree of malignancy of the tumor tissue further increases due to an insufficient supply of oxygen (36). During immunotherapy, the patient experienced an inflammatory response. Inflammatory factors can also induce an abnormally high expression of VEGF (16). Additionally, although anti-vascular therapy is mainly targeted at the central area of tumors, it shows therapeutic resistance around the tumors as well. Anti-vascular therapy can alter the tumor microenvironment through vascular rupture, thereby exerting an anti-tumor effect (34). Evidence suggests that switching to cytotoxic therapy early on may counteract the harmful outbreak of HPD following the use of ICIs (37). The effects of anti-angiogenic drugs compensate for the limitations of the administration of chemotherapy and radiotherapy alone. Hence, the choice of this combination therapy can benefit patients undergoing anti-tumor therapy, to a great extent (36). Therefore, combined therapy with anti-vascular and cytotoxic drugs can be used to control HPD following immunotherapy.

In the present study, following treatment with a combination of anti-angiogenic drugs and biological cytotoxic drugs, the mass was found to have become smaller than before, indicating that the combination of these drugs can control disease progression in patients with HPD to a certain extent, thereby prolonging the survival time of the patients. However, it is still not possible to completely reverse HPD. Hence, the present study provided the following recommendations for ICI treatment.

First, while selecting treatment options, it is necessary to improve TMB and gene detection simultaneously. Additionally, while screening the possible benefits of immunotherapy, one cannot ignore the associated absolute and relative contraindications. Clinicians should inform patients that there are no clinical or biological features that can help predict HPD. At the same time, they should focus on avoiding the application of immunotherapy in potentially high-risk patient populations (patients with large baseline masses, *MDM2/4* and *EGFR* gene mutations and inflammatory reactions), so as not to cause unnecessary reinjury to tumor patients.

Second, during the initial stage of treatment, frequent imaging monitoring and predictive index tests can maximize the benefits of immunotherapy.

Finally, following the application of immunotherapy, clinicians should be fully aware of the subtle changes in the diseases and diagnoses of patients and be able to deal with the adverse reactions associated with immunotherapy, in time. Immunotherapy should be continuously administered to patients who benefit from the treatment, after mild adverse reactions are relieved by other drugs. By contrast, the small population of patients who experience severe adverse reactions and HPD, should stop taking drugs permanently.

It is still necessary to explore how HPD can be accurately identified, evaluated, and processed following immunotherapy, in preparation for the further improvement of the efficiency and safety of immunotherapy in tumor treatment.

In the present case study, the patient developed HPD after undergoing immunotherapy once. Therefore, it is necessary to treat patients using immunotherapy carefully, to screen suitable patients, to try to avoid the occurrence of HPD and pay attention to distinguish between pseudo-progression and hyperprogression. After receiving anti-angiogenic drugs combined with chemotherapy and anti-tumor therapy, the disease was controlled to a certain extent. Therefore, combined therapy can be used as a means of immunotherapy following the occurrence of HPD, in order to control the rate of disease progression and prolong the survival time of patients. Nevertheless, the mechanism and follow-up treatment for hyperprogression following immunotherapy still need to be confirmed by further research.

Acknowledgements

Not applicable.

Funding

This work was supported by grants from the National Natural Science Foundation of China (grant no. 81973677).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SD and KL performed the data analysis, the overall idea design of the study and manuscript writing. RL made substantial

contributions to conception and design. JZ made substantial contributions to acquisition of data and interpretation of data. SD and KL confirm the authenticity of all the raw data. RL and JZ were involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patient provided written informed consent to participate in this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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