# Pembrolizumab induced hyperpigmentation in a patient with lung adenocarcinoma: a case report

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July 5, 2021

**Abstract**

Pembrolizumab is more widespread use clinically with Pembrolizumab being recommended as a first-line therapy for advanced NSCLC. At the same time, some new adverse reactions have also been discovered, including hyperpigmentation. We hereby present a 77-year-old Chinese female with primary bronchial lung cancer. Genetic testing showed negative for EGFR and ALK. Immunohistochemical analysis showed tumor proportion score (TPS) of PD-L1 was 80% on tumor cells. Then the patient received pembrolizumab 200mg every three weeks, as the first-line therapy. Two courses after initiation pembrolizumab, hyperpigmentation appeared on her face and back of the hand. The right middle lobe mass and mediastinal lymph node metastasis progressed after nine courses after initiation of pembrolizumab, and the patient's entire face turned black. It potentially indicates that cutaneous adverse events of hyperpigmentation, might be a negative predictor of response to pembrolizumab in metastatic lung adenocarcinoma patients.

## Introduction

Pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody that binds to the PD-1 receptor, thus blocking immune suppression ligands PD-L1 and PD-L2 from recognizing PD-1 and thereby increasing T-cell immune response against malignant cells. Blocking the PD-1 pathway can inhibit negative immunomodulation caused by PD-1 receptor signaling.[1] Pembrolizumab can reverse T cell suppression and induce anti-tumor response.[2] Pembrolizumab shows significant efficacy in the treatment of non-small cell lung cancer, but it also brings a variety of immune-related adverse reactions.[3] Common adverse reactions reported in the label of Pembrolizumab include fatigue (21%), pruritus (16%), rash (13%), diarrhea (12%) and nausea (10%). A study included 83 patients using pembrolizumab and found that 42% of patients had skin adverse reactions. The most common skin adverse reactions were macular papules (29%), pruritus (12%) and insufficient pigmentation (8%).[4] However, skin hyperpigmentation caused by pembrolizumab is relatively rare in clinical treatment, and the relationship between its occurrence and disease treatment deserves our attention and research.

We describe a rare case of pembrolizumab-associated hyperpigmentation in a patient with lung adenocarcinoma.

## Case report

A 77-year-old female patient was diagnosed with primary bronchial lung cancer (right lung poorly differentiated adenocarcinoma T3N2M1c stage IVB) with metastasis to mediastinal lymph nodes, abdominal cavity and retroperitoneal lymph nodes. Immunohistochemical analysis showed positive staining for CK7, CKpan, Ki67(30%), Vimentin, but negative staining for TTF-1, Napsina, CK5/6, P63, P40, Syn, CD56, CD117, STAT6 and CD34. Additional genetic testing revealed the patient was negative for EGFR, ALK, ROS1, but PD-L1 was positive with 80% of Tumor Proportion Score (TPS). He began an anti-PD-1 therapy with pembrolizumab 200 mg every 3 weeks.

After only two courses of pembrolizumab, the patient noticed slowly worsening painless, non-pruritic, diffuse hyperpigmentation of her face and back of the hand (Fig. B and C). And patient felt fatigue and decreased appetite, but no skin rash. The results of laboratory studies revealed normal liver function, normal kidney function, adrenal function and hemogram during every coursess of pembrolizumab. The hyperpigmentation gradually worsens with the continued use of pembrolizumab, and the patient's entire face turns black after nine courses of pembrolizumab (The patient's family did not provide the photos). The patient died 15 weeks after the first manifestation of hyperpigmentation because food was inhaled into the airway.

The patient had a history of "hypertension" for more than 20 years, and the highest systolic blood pressure was 220mmHg. The patient took perindopril and indapamide tablets (4mg qd) orally regularly, and the blood pressure was well controlled. He had a history of diabetes for more than 10 years, and regularly took metformin sustained-release tablets (0.5g qd), acarbose tablets (50mg tid) and empagliflozin tablets (10mg qd) to hypoglycemic levels, without regular monitoring of blood sugar. And he had "coronary heart disease, atrial fibrillation" medical history more than 10 years.

**Discussion**

Hyperpigmentation is a common dermatologic problem clinically. Hyperpigmentation is defined as the darkening of the skin's natural color, usually due to an increase in melanin deposition in the epidermis or dermis, an increase in chromophores of nonmelanic origin, or to dermal deposition of endogenous or exogenous pigments such as hemosiderin and heavy metals. [5]

Drug-induced hyperpigmentation represents 10 to 20% of all cases of acquired hyperpigmentation.[6] The incidence of drug-induced hyperpigmentation varies according to the drug involved, ranging from isolated cases to 25% of patients receiving a treatment.[5, 7]

Pembrolizumab-induced cutaneous adverse events, including vitiligo,[8, 9] has been described in the literature frequently, but pembrolizumab-induced hyperpigmentation were rarely reported. A study from South Korea included 77 patients who used pembrolizumab reported that one gastric cancer patient developed skin hyperpigmentation after 323 days of pembrolizumab. But it did not specifically describe the occurrence and treatment process of hyperpigmentation.[10]Alexander et al reported two cases of melanoma patients with skin hyperpigmentation after using pembrolizumab. One case reported that a 78-year-old male melanoma patient therapy with pembrolizumab 2mg/kg every 3 weeks and after only 6 weeks (i.e. after two infusions), hyperpigmentation of his face and back as well as melanuria developed. The other one reported that an 85-year-old male melanoma patient therapy with pembrolizumab (2 mg/kg every 3 weeks) and shortly after the first infusion of pembrolizumab, dark gray hyperpigmentation of his face and upper trunk appeared and melanuria developed.[11]Shruti et al also reported that a white man with chronic lymphocytic leukemia in his early 40s developed diffuse hyperpigmentation on the back of pembrolizumab.[12] In summary, the incidence of skin hyperpigmentation caused by pembrolizumab is not high, it is more common on the face, and may occur in the treatment of gastric cancer, melanoma, and chronic lymphocytic leukemia. There are not enough data on the time of occurrence to explain its law. It may occur soon after the first use of pembrolizumab, or it may occur nearly a year or more after use.

In this case, the patient developed hyperpigmentation after using pembrolizumab. The patient did not use other chemotherapeutics or targeted drugs during the use of pembrolizumab, and had no previous skin hyperpigmentation manifestations. The patient started to develop hyperpigmentation after two courses of pembrolizumab treatment, and then gradually darkened on the face and back of the hands with the pem-

brolizumab treatment. The patient didn't have a history of chronic sun exposure during the pembrolizumab treatment. We applied the Naranjo adverse drug reaction (ADR) scale in the present study,[13] the result indicated a probable ADR caused by pembrolizumab therapy, with a score of 8(Table 1).

The mechanism of pembrolizumab-induced hyperpigmentation is unclear. It may be caused by increased synthesis of melanin, increased synthesis of lipofuscin, or deposition of drug-related substances on the skin.[14] It may also be caused by melanoma cells releasing melanocyte peptide growth factors, such as α-melanocyte stimulating hormone, hepatocyte growth factor and endothelin-1in patients with melanoma.[15, 16]In addition, there is also a view that skin immune-related adverse vents (irAEs) caused by Cutaneous Toxicities of immune checkpoint inhibitors (ICIs) are due to the excessive activation of the immune system mediated by ICIs, which is the same as its anti-tumor effect.[17] Nazanin Majd et al reported that skin pigmentation is closely related to the abnormal increase of ACTH,[18] but in our reported case, the ACTH test did not increase abnormally.

In this case, the patient used pembrolizumab once in this hospital and then returned to the local hospital for continued treatment. We can't evaluate the patient's treatment effect during this treatment period for the patient refuses to have a CT examination. When the patient returned to the hospital for treatment 6 months later, the patient had already developed hyperpigmentation. At this time, the patient's tumor had progressed. Therefore, we failed to follow up and evaluate the patient's treatment effect. The patient developed hyperpigmentation after two courses of pembrolizumab treatment, and slowly worsening. The relationship between hyperpigmentation and pembrolizumab treatment on lung adenocarcinoma is unclear now.

Sanlorenzo et al found that skin adverse reactions occurred after the use of pembrolizumab, especially hypopigmentation when pembrolizumab was used to treat melanoma patients, which may indicate a better therapeutic effect.[4] Conversely, Alexander Thiema et all reported that hyperpigmentation is a condition that may be a negative predictor of response to pembrolizumab treatment for melanoma patients.[11, 12] Thus, we speculate that cutaneous adverse events of hyperpigmentation, might be a negative predictor of response to pembrolizumab in metastatic lung adenocarcinoma patients.

**Acknowledgment**

We express our sincere gratitude to the patient's family who provided images assistance for this project.

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Table 1 ADR probability scale

| To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score. | To assess t |
|---|---|
| | Yes |
| 1.Are there previous conclusive reports on this reaction? | +1 |
| 2.Did the adverse event appear after the suspected drug was administered? | +2 |
| 3.Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered? | +1 |
| 4. Did the adverse reaction reappear when the drug was readministered? | +2 |
| 5. Are there alternative causes (other than the drug) that could on their own have caused the reaction? | -1 |
| 6. Did the reaction reappear when a placebo was given? | -1 |
| 7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic? | +1 |
| 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | +1 |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | +1 |
| 10. Was the adverse event confirmed by any objective evidence? | +1 |
| Total score | Total score |

Note. definite [?]9, probable 5 to 8, possible 1 to 4, doubtful [?]0.

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