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Case Report

Rapid Disease Progression of Advanced Non-small Cell Lung Cancer Five Months after Cessation of Pembrolizumab

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We report a case of late-onset hyperprogressive disease after cessation of a PD-1 inhibitor. A male was diagnosed with metastatic lung adenocarcinoma with little progression for 2 months before treatment. He received pembrolizumab as a second-line treatment and was subsequently prescribed docetaxel for 3 months until a slight increase in pleural effusion. At the time of progression to docetaxel, he commenced prednisolone because of immune-system-related diarrhea. After that, his general condition rapidly worsened with severe fatigue and hypoxia. Computed tomography revealed a massive increase of pleural effusion and replacement of almost the entire liver with cancer over a period of 5 weeks.

Key words: lung cancer, immune checkpoint inhibitors, pembrolizumab, hyperprogression

Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors are currently the standard treatments for advanced NSCLC. Unlike conventional therapies, immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 inhibitors sometimes induce atypical tumor responses including pseudoprogression and hyperprogressive disease (HPD). HPD is defined as a greater than two-fold increase in the tumor growth rate (TGR) of patients exhibiting disease progression [1,2]. HPD is caused not only by PD-1/PD-L1 inhibitors but also, less frequently, by cytotoxic T lymphocyte associated antigen-4 (CTLA-4) inhibitors [3]. HPD is usually observed soon after prescription of immune checkpoint inhibitors [4]; to the best of our knowledge, there has been no report on late-onset HPD. We here report a case of late-onset rapid disease progression of advanced NSCLC at 5 months after cessation of pembrolizumab; the disease course was thus distinct from conventional HPD.

Case

A male in the sixth decade of life was diagnosed with advanced pulmonary adenocarcinoma; the PD-L1 tumor proportion score was 5%. The progression rate was relatively mild; little progression was evident for 2 months prior to treatment commencement. Pembrolizumab was prescribed as a second-line treatment following platinum doublet chemotherapy. This significantly inhibited tumor growth for 11 months, despite a 3-month cessation of therapy because of immune-related adverse events (irAEs). Then, sternal and vertebral metastases developed. Docetaxel was administered as a third-line therapy for 4 months; the pleural effusion increased slightly and a small liver metastasis

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developed. Just prior to docetaxel cessation, he commenced oral prednisolone because of sustained immune system-related grade 2 diarrhea over 1 month in duration. Although the diarrhea disappeared within a few days of prednisolone prescription, his general condition rapidly worsened, accompanied by severe fatigue, and he underwent emergency hospitalization because of hypoxia. Contrast-enhanced computed tomography showed that the pleural effusion had increased massively and almost the entire liver was replaced with cancer over 5 weeks; the progression rate had been relatively slow prior to prednisolone commencement (Fig. 1 and Fig. 2). Pleurocentesis revealed a class V adenocarcinoma, confirming that progression was attributable to lung cancer.

Discussion

We experienced a case of rapid disease progression of advanced NSCLC 5 months after cessation of pembrolizumab. The disease course seemed to accelerate greatly (considering the prior progression rate) (Fig. 2); we diagnosed this as HPD caused by prior pembrolizumab. Our case differs from conventional HPD patients in two ways. One is that HPD developed after pembrolizumab cessation, rather than during treatment. PD-1 inhibitors bind to lymphocytes for at least several months after drug cessation [5], and may thus exert various effects long-term. Prior to HPD development, our patient developed sustained diarrhea caused by irAEs, and required steroid therapy, suggesting that pembrolizumab remained in the body for a long time after drug cessation. The other unique feature of our current case is that the patient initially responded to pembrolizumab before developing HPD. All previously reported HPD cases exhibited rapid progression in the absence of any response to PD-1/PD-L1 inhibitors. Although the precise mechanism of HPD remains unclear, one hypothesis is that HPD may be caused by a change in polarization of immunosuppressive cells modulated by PD-1/PD-L1 inhibitors [6]. In our current case, disease progression seemed to accelerate after steroid therapy for diarrhea (Fig. 1). Such therapy might have modulated immune cell polarization, causing formerly immuno-activating cells to become immunosuppressive. We propose that steroid therapy runs a risk of triggering late-onset HPD phenomena.

In conclusion, we experienced a case of rapid disease progression of advanced NSCLC 5 months after cessation of pembrolizumab. We propose that this be considered a case of late-onset HPD after cessation of immune checkpoint therapy.

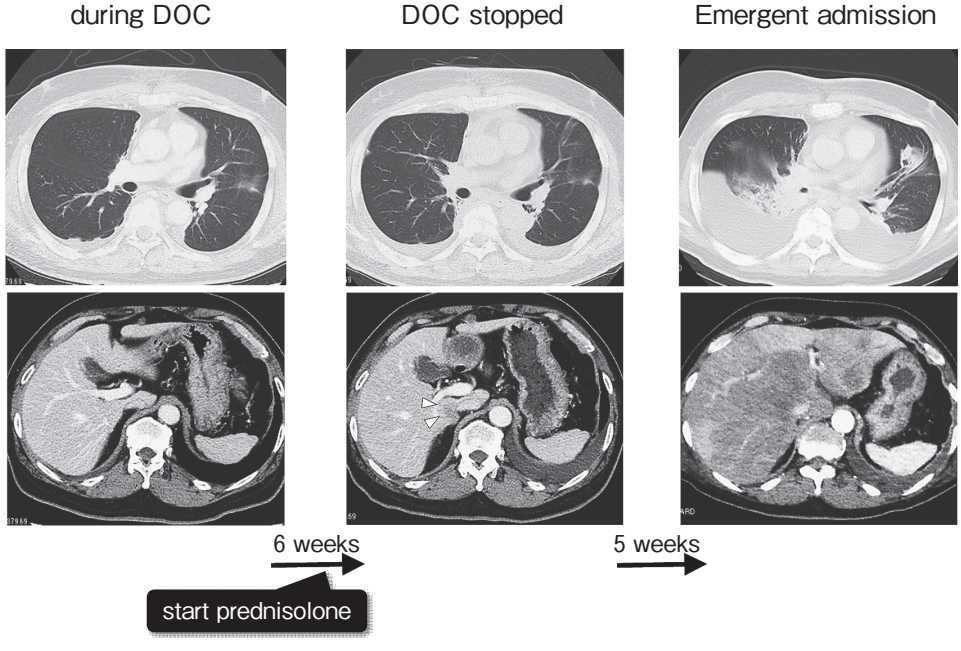

Fig. 1 Treatment progression and TGR.

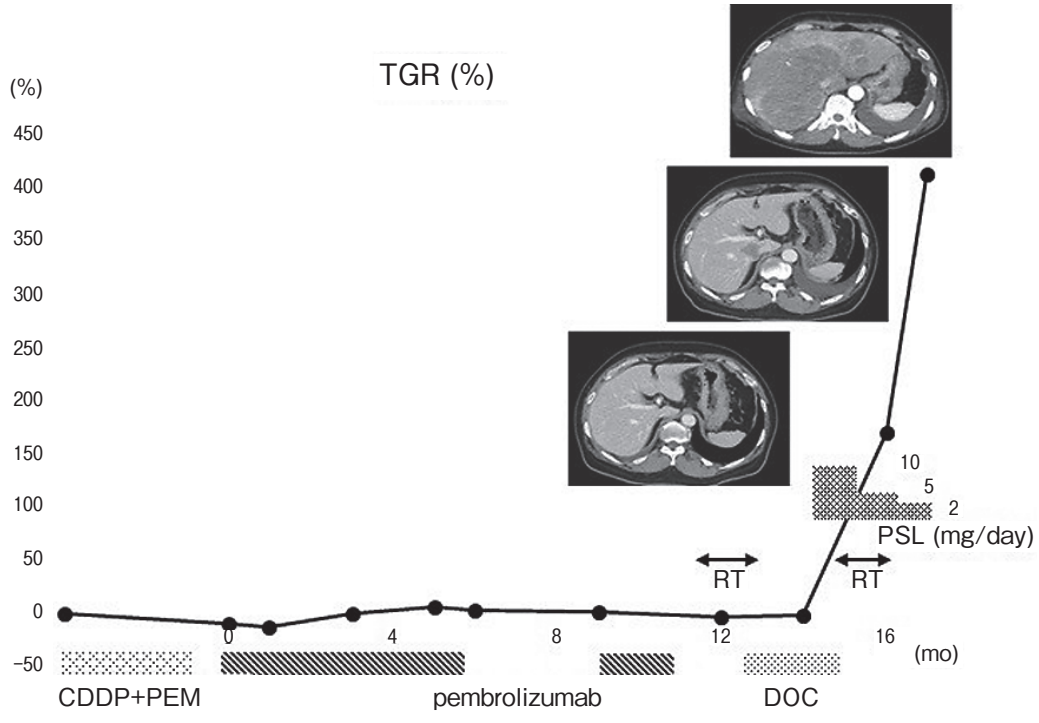

Fig. 2 Computed tomography showing rapid tumor growth after initiation of steroid.

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