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CASE REPORT

Compromise or not? A case report of successful treatment of pembrolizumab-induced hepatitis in a patient with non-small cell lung cancer with low-dose methylprednisolone and bicyclol

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Keywords
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Abstract

Pembrolizumab, an anti-programmed cell death protein 1 (PD-1) antibody, has been shown to improve survival in patients with non-small cell lung cancer (NSCLC) with high expression of programmed death-ligand 1 (PD-L1). Corticosteroids are the mainstay for most high-grade immune-related adverse events (irAEs) such as pembrolizumab-induced hepatitis. However, the dose and duration of corticosteroid therapy are not well defined. The objective of this case report was to describe a new treatment pattern for severe immune checkpoint inhibitor-associated hepatitis. Here, we report the case of a patient with metastatic lung adenocarcinoma who developed grade 3 immunotherapy-induced hepatitis after the first cycle of pembrolizumab. Alanine aminotransferase (ALT) levels peaked at 233 U/L. Hepatitis was alleviated after the administration of methylprednisolone. Therefore, we retreated the patient with pembrolizumab. However, aminotransferase levels increased again after the initiation of low-dose methylprednisolone or the reuse of pembrolizumab. Finally, hepatitis was controlled with low-dose methylprednisolone plus bicyclol, a Chinese hepatoprotective agent. Although the patient had been on low-dose methylprednisolone therapy for about six months, he showed a prompt response. During this period, we also found a dramatic decrease in the neutrophil-lymphocyte ratio (NLR), senescent T cells ($CD8^+CD28^-CD57^+$), and myeloid-derived suppressor cells (MDSCs) in the peripheral blood of the patient. To our knowledge, this is the first case report of successful management of grade 3 pembrolizumab-induced hepatitis with a combination of low-dose corticosteroids and bicyclol. The durable clinical response and changes in blood biomarkers indicate that low doses of corticosteroids do not compromise the efficacy of immune checkpoint inhibitors (ICIs). Therefore, this case may provide a new treatment pattern for severe immunotherapy-induced hepatitis.

Introduction

Immune checkpoint inhibitors (ICIs), such as the anti-programmed cell death protein 1 (PD-1) agent pembrolizumab, have shown favorable response and durable clinical benefit in patients with advanced non-small cell lung cancer (NSCLC). Therefore, it has become a standard of care in patients with advanced NSCLC with high programmed death-ligand 1 (PD-L1) expression.[1, 2] However, the management of immune-related adverse events (irAEs) such as pembrolizumab-induced hepatitis present a

challenge.[3] Permanent discontinuation of ICIs and systemic corticosteroid therapy are recommended in patients with severe immunotherapy-induced hepatitis.[3–5] Corticosteroids, as potent and broad-spectrum immune suppressors, may compromise antitumor immune responses elicited by ICIs. Therefore, the dose and duration of corticosteroid therapy should be optimized in the management of severe immunotherapy-induced hepatitis. It is also unclear whether hepatoprotective agents are useful in patients with immunotherapy-induced hepatitis. Here, we report a case of successful retreatment of severe pembrolizumab-induced hepatitis in a patient with NSCLC with a combination of methylprednisolone and bicyclol (hepatoprotective agent) We explored the changes in senescent T cells, myeloid-derived suppressor cells (MDSCs), and inflammatory cytokines after corticosteroid administration.

Case report

A 68-year-old Chinese man, an ex-smoker with a 40 pack-year history (quit three years ago), initially presented with low-grade fever, intermittent cough, yellow sticky sputum, and bilateral neck masses in August 2018. Chest computed tomography (CT) scan showed an irregular mass in the middle lobe of the right lung, swollen bilateral hilar and mediastinal lymph nodes, and right inferior pulmonary embolism. Histologic examination of an initial bronchoscopic biopsy showed poorly differentiated lung adenocarcinoma (Fig 1a,b). Immunohistochemistry studies revealed that PD-L1 (clone SP142) was highly expressed in the tumor cells (tumor proportion score [TPS] was about 70%, Fig 1c) and approximately 40% of the tumor-infiltrating cells had PD-1 expression (clone NAT105, Fig 1d). Next-generation sequencing revealed that this patient had a high tumor mutational burden (TMB, 20.7 mut/Mb, Nanjin Geneseeq Technology Inc.) with no alteration in EGFR, EML4-ALK, ROS-1, c-MET, and BARF. The fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) scan revealed an irregular mass in the right middle lobe, right adrenal gland metastatic nodule, splenic metastatic nodule, and lymph node metastasis of the bilateral neck, supraclavicular region, right axilla, mediastinum, hilar, and retroperitoneum (Fig 3a). Contrast-enhanced magnetic resonance imaging (MRI) of the brain showed no abnormalities. Therefore, this patient was staged as cT3N3M1c (IVB).

The patient received the first cycle of pembrolizumab 200 mg intravenously without contraindications on 9 November 2018 (Fig 2a), based on KEYNOTE-024[1] and continuous treatment with enoxaparin (6000 IU per time, subcutaneous injection, every 12 hours) for pulmonary embolism. Alanine aminotransferase (ALT) levels increased from 59 units per liter (U/L) before treatment to 132 U/L (reference range: 15–40 U/L) on day 7, with aspartate aminotransferase (AST) levels of 53 U/L (reference range: 15–40 U/L) and alkaline phosphatase (ALP) levels of 296 U/L (reference range: 45–125 U/L). Although the patient received immediate outpatient therapy with diammonium glycyrrhizinate and polyene phosphatidylcholine, the ALT, AST, and ALP levels peaked at 233 U/L, 89 U/L, and 296 U/L, respectively, 13 days after pembrolizumab infusions (Fig 2b, Table 1), reflecting a grade 3 (severe) elevation in ALT levels as per Common Toxicity Criteria for Adverse Events, Version 4.0 (CTCAEv4.0).[6] His synthetic liver function remained intact, with normal bilirubin, albumin, and blood coagulation function. There were no clinical or biochemical signs of acute liver failure, such as jaundice, coagulopathy, hepatomegaly, or hepatorenal syndrome.

There was no history of chronic liver disease, alcohol consumption, intravenous drug use, the use of other medications or herbal supplements. A comprehensive screening was performed to evaluate the potential causes of hepatitis. Serologies for hepatitis A, B, C, and E were negative. Autoimmune tests for antismooth muscle antibody (Ab), antimitochondrial Ab, antiparietal cell Ab, antiliver and kidney microsomal Ab, anticardiac Ab, and antimitochondrial Ab M2 subtypes were also negative. Antinuclear antibody was mildly elevated at 1:160 (cytoplasmic type), but it was not considered clinically significant in this setting. Ultrasound showed that the liver was normal in shape and size, with no evidence of hepatic lesions or fibrosis. Finally, the patient was admitted for grade 3 ICI-induced hepatitis, according to CTCAEv4.0.[6]

Treatment for hepatitis was initiated with methylprednisolone at 0.5 mg/kg (intravenous 40 mg per day, Fig 2a). ALT levels decreased to 145 U/L with AST levels of 49 U/L and ALP levels of 144 U/L after six days of intravenous methylprednisolone. Intravenous methylprednisolone was discontinued and changed to an oral form at 20 mg and 12 mg/day for six days, followed by 8 mg/day. However, ALT levels returned to 201 U/L. Considering that long-term high-dose corticosteroids would compromise the efficacy of immunotherapy,[7] bicyclol, a Chinese hepatoprotective agent, was added at 50 mg three times per day without adjusting the dose of methylprednisolone. Elevated ALT levels rapidly resolved to 52 U/L 7 days later, and bicyclol was discontinued on day 40 (Fig 2). The patient reported significant improvement in physical activity. Physical examination showed that supraclavicular lymph node metastasis had dramatically shrunk in size and disappeared one month after the first cycle of pembrolizumab. Therefore, the patient received retreatment with pembrolizumab on day 38. During this period, ALT levels were well-controlled with 8 mg methylprednisolone and were only increased to 159 U/L on day 54 (Fig 2). CT scan showed a significant decrease in the

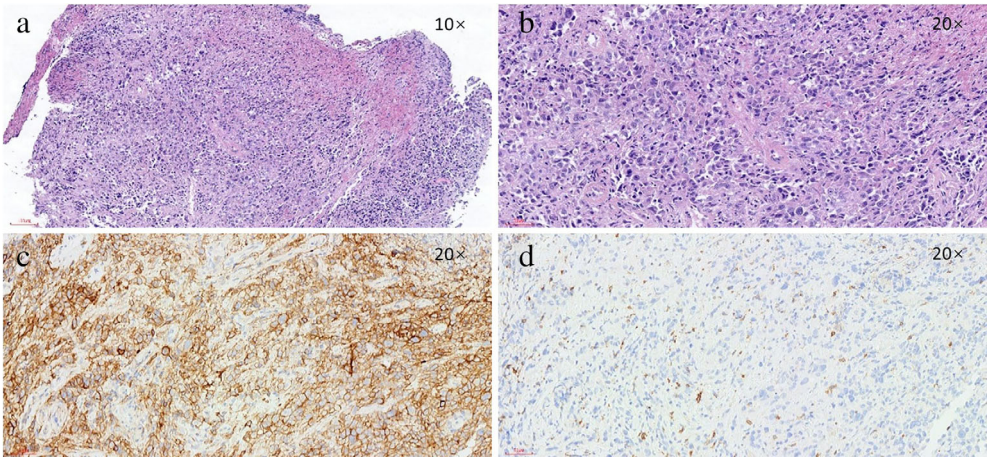

Figure 1 Representative hematoxylin-eosin (H&E) stained images and immunohistochemistry (IHC) results of PD-L1 and PD-1 in bronchial mucosal biopsy specimens before pembrolizumab treatment. (**a**, **b**) Representative H&E staining patterns of formalin-fixed, paraffin-embedded primary NSCLC lesions. (**c**) PD-L1 IHC staining (clone SP142) showed strongly positive PD-L1 expression in 70% of viable tumor cells. (**d**) PD-1 IHC staining (clone NAT105) showed that the positive rate of PD-1 expression in tumor-infiltrating lymphocytes was around 40%. Magnification is indicated.

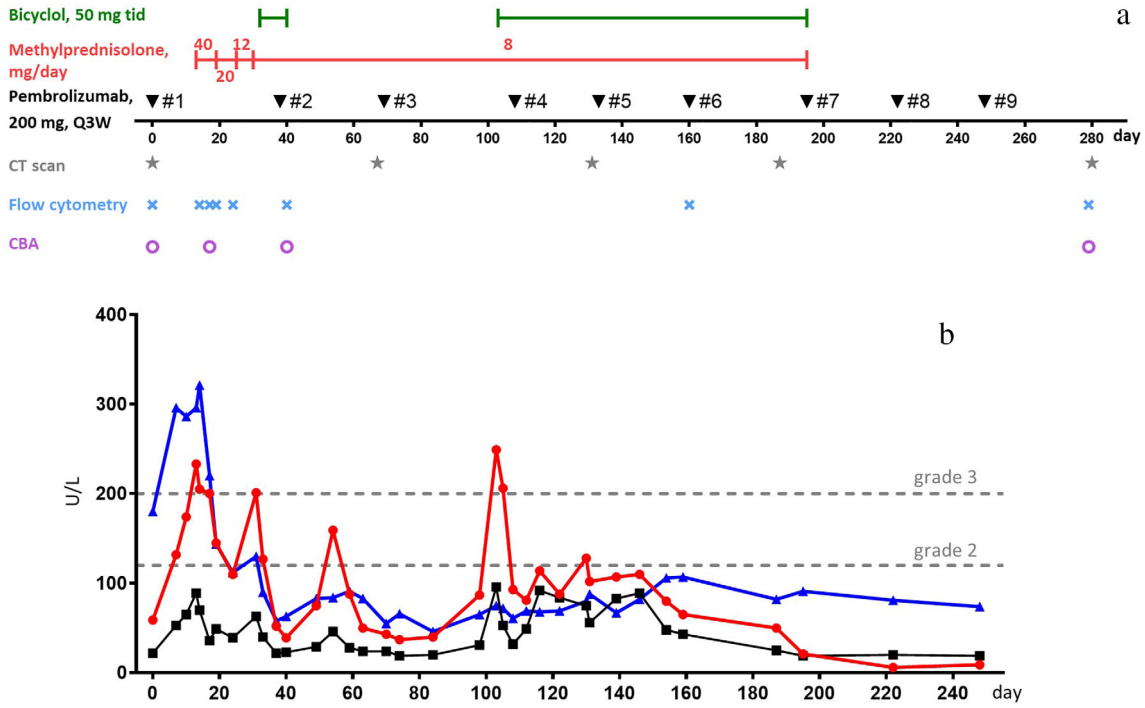

Figure 2 Summary of the clinical treatment and liver function tests of the patient. (**a**) Diagram of various therapeutic interventions and clinical examinations received by this patient. The symbols indicate the time points for each intervention. Day 0 represents the day the patient received the first pembrolizumab treatment. CBA, cytometric bead array (**b**) Levels of serum alanine aminotransferase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) were used to monitor liver function (—●—) ALT (U/L), (—■—) AST (U/L), (—▲—) ALP (U/L). Grade 2 was defined as >3× upper normal limit (ULN, 120 U/L) and grade 3 > 5× ULN (200 U/L).

size of known tumors in the right lung mass, the right adrenal gland metastatic nodule, and the mediastinal lymph nodes on day 67. The splenic metastatic nodule had completely disappeared (Fig 3a,b). ALT levels increased

Table 1 Laboratory data during treatment of pembrolizumab

Time until onset	d0	d7	d13	d19	d24	d31	d37	d54	d70	d103	d108	d131	d159	d187	d222	d248
ALT	59	132	233	145	110	201	52	159	43	249	93	102	65	50	6	9
AST	22	53	89	49	39	63	22	46	24	96	32	56	43	25	20	19
ALP	180	296	296	144	112	130	58	84	55	75	61	88	107	82	81	74
Leukocyte	14.37		10.5	12.96	11.3		9.85		8.64	8.67	8.59	9.94	12.07	10.47	9.6	8.5
Lymphocyte	1.07		2.27	2.6	3.35		3.12		2.85	1.99	2.48	2.49	1.89	2.17	2.6	2.42
Neutrophil	8.16		5.93	8.02	86.41		5.53		4.88	5.61	5.37	6.48	9.22	7.33	5.88	5.11
SCC	2.7	1.8							0.4	0.6		0.5	0.8	0.8	1.3	
Cyfra21-1	46.51	42.9							4.43	2.81		2.7	2.41	2.42	2.51	
CEA	3.99	4.22							5.3	4.86		4.17	4.53	5.41	4.05	

ALT, serum alanine aminotransferase (reference range: 15–40 U/L); AST, aspartate transaminase (15–40 U/L); ALP, alkaline phosphatase (45–125 U/L); leukocyte (3.5–9.5 × 10^9/L); lymphocyte (1.1–3.2 × 10^9/L); neutrophil (1.8–6.3 × 10^9/L); SCC, squamous cell carcinoma antigen (≤1.5 ng/mL); Cyfra21-1, soluble fragment of cytokeratin19 (0–3.3 ng/mL); CEA, carcinoembryonic antigen (0–5 ng/mL).

again to 249 U/L on day 103, followed by a gradual decrease to normal levels after the addition of bicyclol. The patient did not experience recurrence of hepatitis, even after the withdrawal of methylprednisolone and bicyclol on day 195 (Fig 2). After nine cycles of pembrolizumab, the treatment response was assessed by durable partial remission (50% reduction), based on radiographic assessment and resolution of pulmonary embolism (Fig 3).

Blood count tests showed a high pretreatment neutrophil-to-lymphocyte ratio (NLR) (Fig 4a,b, Table 1), indicating a poor outcome.[8] However, 14 days after the initiation of pembrolizumab treatment, an increased lymphocyte count and a decreased neutrophil count resulted in a dramatic decrease in NLR detected in the peripheral blood (Fig 4a,b, Table 1), which was associated with a better outcome.[8] The levels of proinflammatory cytokines IL-6 and TNF-α were upregulated with the onset of hepatitis and returned to normal when hepatitis was controlled (Fig 4f). The absolute number of lymphocytes and neutrophils, NLR, and the percentage of $CD8^+$ and $CD4^+$ T cells was not significantly affected by hepatitis or methylprednisolone administration (Fig 4a,b,c). However, the production of granzyme B and IFN-γ in $CD8^+$ T cells was diminished by one-third after the administration of high doses of methylprednisolone and restored when the dosage of methylprednisolone was reduced to 8 mg/day, while granzyme B^+ and IFN-γ^+ $CD4^+$ T cells were not alerted (Fig 4d,e). The levels of IFN-γ and IL-2 in the plasma were elevated after retreatment with pembrolizumab (Fig 4f). These results indicated that the antitumor activity of T cells was impaired with high, but not low-dose methylprednisolone. In accordance with previous reports,[8, 9] we also found a reduction in senescent T cells (Fig 4g) and MDSCs (Fig 4h), and two biomarkers associated with better outcomes, in the peripheral blood during treatment. These results indicated that long-term low doses of methylprednisolone combined with bicyclol to control pembrolizumab-induced hepatitis did not affect ICI efficacy.

Discussion

Single-agent pembrolizumab is recommended as first-line therapy for advanced NSCLC patients with high PD-L1 expression (TPS > 50%), negative or unknown test results for *EGFR*, *BRAF V600E* mutations, ALK, and ROS1 rearrangements based on the KEYNOTE-024 study.[1] It is well-known that the detection of PD-L1 expression by immunohistochemistry with 22C3 monoclonal antibody (McAb) is a concomitant diagnosis of single-agent pembrolizumab application. However, the 22C3 McAb has not been approved in China. Considering that the proportion of tumor staining cells with SP142 McAb was lower

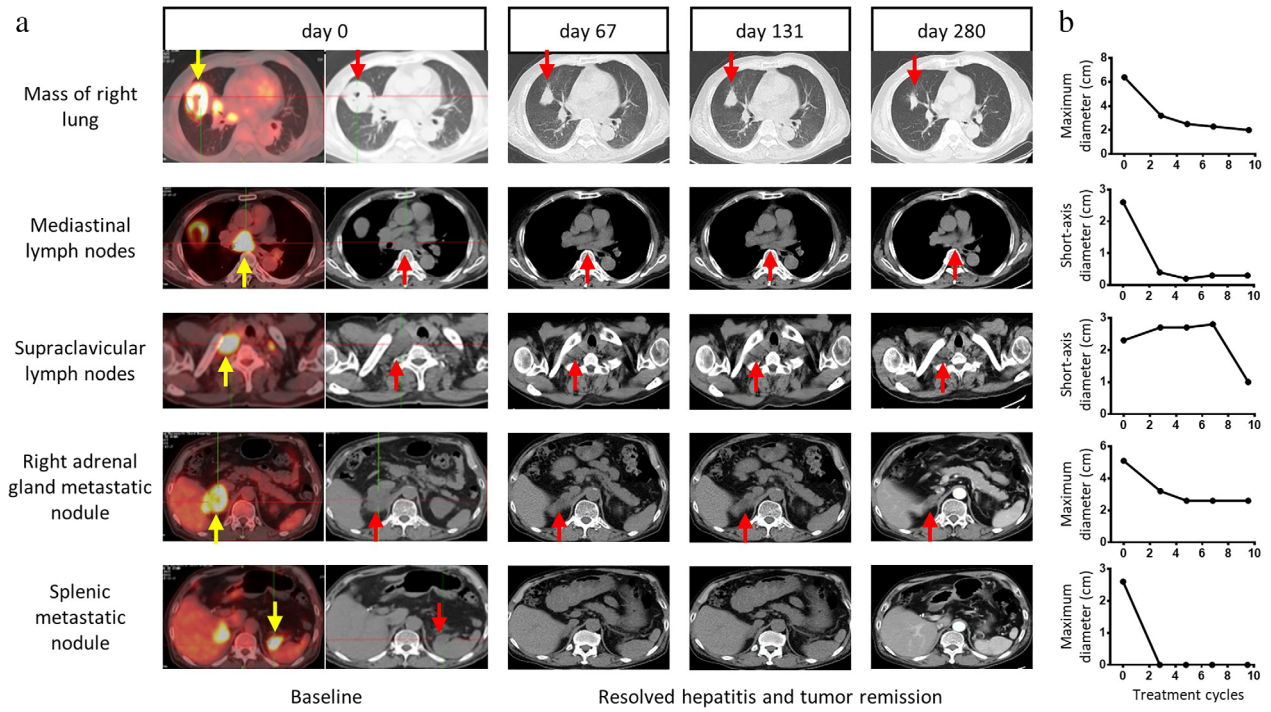

Figure 3 Monitoring tumor response to pembrolizumab. (**a**) Representative fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) and CT images of tumor nodules before and after pembrolizumab therapy. Arrows point to the tumor nodules, including the mass in the right lung, mediastinal lymph nodes, supraclavicular lymph nodes, right adrenal gland metastatic nodule, and splenic metastatic nodule. (**b**) Measurement of tumor diameter changes after two, four, six, and nine cycles of pembrolizumab treatment as in (**a**).

than that of 22C3 McAb,[10, 11] we speculate that PD-L1 expression detected by 22C3-IHC assay in our patient may be higher than what we observed by SP142-IHC assay. Therefore, we administered pembrolizumab as first-line treatment.

Our patient developed grade 3 immune-related hepatitis on day 13 after the initiation of pembrolizumab. Immune-related hepatitis is mostly mild but may be fatal in rare cases. The incidence of immune-related hepatotoxicity is estimated to be 0.7% to 1.8% for PD-1/PD-L1 inhibitors,[12] but at 14.3% for pembrolizumab, according to a retrospective study.[13] The overall incidence of any grade of hepatitis was 18% in the Checkmate 078 study[14] and 6% in the CheckMate 017 and CheckMate 057 study with nivolumab-treated NSCLC patients,[15] which suggests that Chinese patients may be prone to liver injury after immunotherapy. Asymptomatic elevations of ALT and AST levels are the most common clinical manifestations, and the median onset time is usually 5–6 weeks after the initiation of treatment.[12] Considering the early onset of immune-related hepatitis in this patient, pembrolizumab was discontinued, and corticosteroids were promptly administered to manage hepatitis according to the NCCN and ESMO guidelines.[3, 4]

As corticosteroids are potent and broad-spectrum immune suppressors,[16] their role in suppressing antitumor immune responses elicited by ICIs is under debate. Early retrospective analyses revealed that corticosteroids used in the management of adverse effects during immunotherapy did not affect time to failure (TTF) and overall survival (OS).[17, 18] However, analysis of another cohort of melanoma patients who experienced ipilimumab-induced hypophysitis and were managed with corticosteroids revealed that TTF and OS significantly decreased in the high-dose group (prednisone >7.5 mg/day) than in the low-dose group (prednisone <7.5 mg/day).[7] In our patient, granzyme B^+ and IFN-γ^+ $CD8^+$ T quickly diminished, indicating impaired cytotoxicity at a high dose of methylprednisolone and were restored at a low dose of methylprednisolone, suggesting that a high dose of corticosteroids could inhibit ICI efficacy. Therefore, to maintain ICI efficacy, the dosage of methylprednisolone was promptly reduced to 8 mg/day after hepatitis was controlled, and it did not increase even when ALT levels increased again.

As IL-6 and TNF-α were significantly increased in autoimmune liver disease,[19] we speculated that the elevation of IL-6 and TNF-α observed in our patient may contribute to the pathology of pembrolizumab-induced hepatitis. In

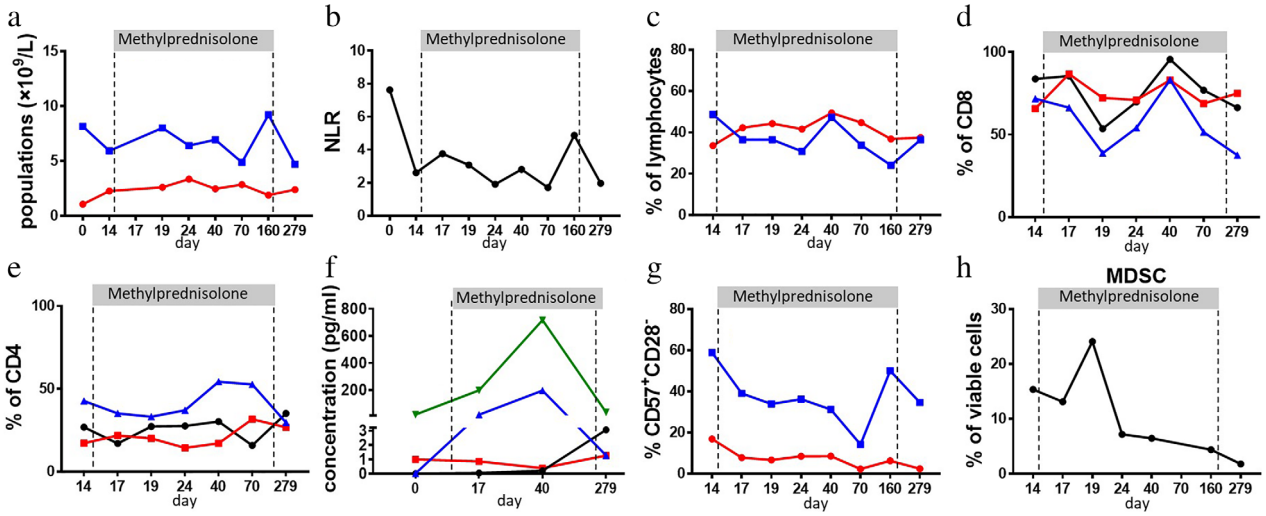

Figure 4 Changes in immune signature from peripheral blood during pembrolizumab treatment. Line chart shows changes in phenotype and function of leukocytes collected from peripheral blood at the indicated time points. The x-axis represents days after the initiation of pembrolizumab treatment. (**a**) Density (×10^9/L) of neutrophils and lymphocytes (–■–) Neutrophil, (–●–) Lymphocyte. (**b**) Neutrophil-to-lymphocyte ratio (NLR) (**c**) The percentage of $CD8^+$ and $CD4^+$ T cell subsets in lymphocytes (–■–) CD8, (–●–) CD4. (**d**, **e**) The percentage of $CD8^+$ T cells (**d**) (–●–) IFN-γ, (–■–) GzmB, (–▲–) TNF-α and $CD4^+$ T cells (**e**) expressing indicated cytokines after stimulation with PMA and ionomycin (–●–) IFN-γ, (–■–) GzmB, (–▲–) TNF-α. (**f**) The concentrations of IL-6, TNF-α, IL-2, and IFN-γ in the serum were detected by cytometric bead array (CBA) (–▼–) IL-6, (–▲–) TNF-α, (–■–) IL-2, (–●–) IFN-γ. (**g**) The percentage of senescent T cells ($CD57^+CD28^-$) in $CD8^+$ and $CD4^+$ T cells (–■–) CD8, (–●–) CD4. (**h**) The percentage of MDSCs ($HLA\text{-}DR^-CD11b^+CD33^+$) within viable cells. Methylprednisolone used to control hepatitis is indicated above the graphs.

irAEs, such as diarrhea and colitis, infliximab, a form of TNF-α inhibitor, is recommended. We did not attempt to use infliximab as it may cause idiosyncratic liver failure.[3, 4] Bicyclol is a hepatoprotective agent used for the treatment of drug-induced liver injury (DILI), as recommended in Chinese guidelines.[20] It attenuates liver inflammation via repression of ROS-activated NF-κB, suppresses the production of TNF-α in hepatocytes, and normalizes ALT levels in chronic hepatitis B patients.[21, 22] In our patient, bicyclol was safe and effective in reducing the levels of ALT and proinflammatory cytokines IL-6 and TNF-α. However, further studies are needed to determine the role of bicyclol in the management of immunotherapy-induced hepatitis.

The safety and efficacy of retreatment with ICIs after irAEs in patients with NSCLC is unclear. In a small cohort study, Fernando *et al.* suggested that 74% of the patients had either no irAEs or mild and manageable irAEs after retreatment. In patients with objective responses before the irAEs, PFS and OS were similar in the retreatment and discontinuation cohorts.[23] However, this result may not be convincing, as the cohort size is relatively small. Considering the very early onset of immunotherapy-related hepatitis, we retreated the patient with pembrolizumab when hepatitis was controlled to grade 1 with methylprednisolone administration (Fig 2). Fortunately, an increase in anti-tumor cytokines IL-2 and IFN-γ was detected after pembrolizumab therapy (Fig 4f), and the patient showed partial remission (Fig 3). Further research is warranted to identify other biomarkers to assist in retreatment with immunotherapy after irAEs.

Recent research has demonstrated that subsets of T cells exhibit different sensitivities to methylprednisolone. Amber JG reported that naïve T cells were more affected by dexamethasone with increased apoptosis and decreased proliferation ability than memory T cells.[24] In a mouse model, early administration of corticosteroids impaired low but not high-affinity CD8 memory T cells that reacted to neoantigens in the tumor. In melanoma patients treated with cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blockade, overall survival was shorter in patients with low TMB who received early corticosteroids, but not in patients with high TMB.[25] Based on the above research, high TMB (20.7 mut/Mb)[2] in this patient was probably the reason why the antitumor efficacy of pembrolizumab was not affected by the early use of corticosteroids. Further studies are required to confirm this hypothesis.

Several peripheral blood biomarkers were applied at baseline or on treatment to predict responses to checkpoint blockade.[8, 9] As methylprednisolone has a broad impact on the number and function of immune cells, the role of the immune-based biomarkers in NSCLC patients receiving pembrolizumab therapy and corticosteroids is unclear. In our case, NLR, MDSCs, and senescent T cells ($CD8^+CD28^-CD57^+$) showed a tendency to decrease

indicating that they were not affected by low-dose methylprednisolone treatment. Further exploration and validation of the effect of methylprednisolone on the predictive efficacy of these immune-related biomarkers are warranted.

In conclusion, here we report the successful management of grade 3 pembrolizumab-induced hepatitis with a combination of low-dose corticosteroids and bicyclol. The durable clinical response and changes in blood biomarkers indicate that low doses of corticosteroids do not compromise the efficacy of ICIs. This case suggests that hepatoprotective agents may help ameliorate ICI-induced hepatitis. Further prospective controlled studies are needed to assess new management strategies for immune-related hepatitis.

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Disclosure

The authors declare no conflict of interest in this work.

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