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【 CASE REPORT 】

Hemophagocytic Lymphohistiocytosis in a Patient with Rheumatoid Arthritis on Pembrolizumab for Lung Adenocarcinoma

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Abstract:
Immune checkpoint inhibitors have changed the landscape of classic cancer treatment. However, their use is associated with the emergence of new adverse events. An elderly man with rheumatoid arthritis was started on pembrolizumab for newly diagnosed advanced lung cancer. He subsequently developed hemophagocytic lymphohistiocytosis (HLH), which is potentially fatal but has not been properly established as an immune checkpoint inhibition-induced event. We herein report the case of a patient with pembrolizumab-induced HLH.

Key words: pembrolizumab, hemophagocytic lymphohistiocytosis, immune checkpoint inhibitors, lung cancer, rheumatoid arthritis, immune-related adverse event

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Introduction

Immune checkpoint inhibitors (ICIs) have now become a treatment alternative for a wide range of cancer types. Although they have demonstrated substantial clinical benefits, they have also revealed the new concept of immune-related adverse events (irAEs). Common manifestations include dermatitis, arthritis, endocrinopathy, and hepatitis, and any organ can be affected. Besides non-fatal adverse events, ICIs are reported to occasionally elicit life-threatening conditions, such as myocarditis, pneumonitis, and enterocolitis (1, 2). Hemophagocytic lymphohistiocytosis (HLH) is a fatal condition triggered by various immune-activating events; however, HLH has been rarely reported in the context of lung cancer immunotherapy. We herein report a case of severe HLH developing in an elderly man with rheumatoid arthritis during lung adenocarcinoma treatment with pembrolizumab.

Case Report

A 74-year-old man was diagnosed with rheumatoid arthritis 1 year before presenting to our hospital. He had been successfully treated for rheumatoid arthritis with low-dose oral methotrexate of 6 mg per week. The man visited our hospital for the evaluation of a lung nodule incidentally found on a medical checkup.

Chest computed tomography (CT) revealed an irregularly marginated nodule with pleural indentation in the right lower lobe and several enlarged mediastinal and subclavian lymph nodes (Fig. 1a-c). Endobronchial ultrasound-guided transbronchial needle aspiration was performed; the pathological findings of the specimen indicated the diagnosis of lung adenocarcinoma.

The lung cancer was staged as ⅢB, T2aN3M0. Immunohistochemistry was negative for both *EGFR* and *ALK* mutations, and 60% of the tumor cells were positive for programmed death ligand-1 (PD-L1). Immunotherapy with pembrolizumab was chosen over chemoradiotherapy because

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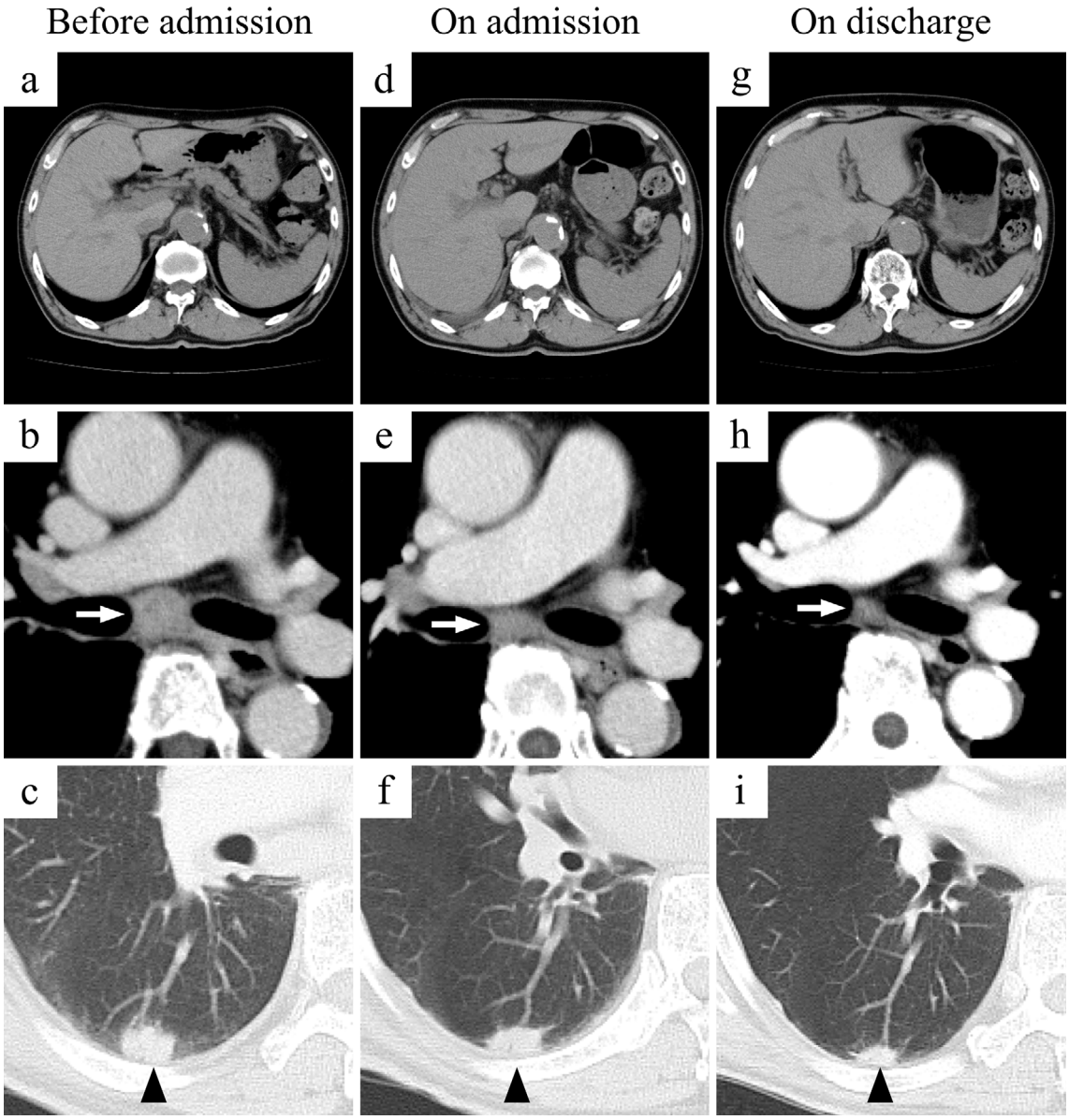

Figure 1. **Changes in CT findings. The upper panels show the liver and spleen: (a) No abnormal liver or spleen findings were seen before admission. (d) Hepatosplenomegaly was detected on admission. (g) The liver and spleen sizes normalized before discharge. The middle panels show the inferior tracheobronchial lymph nodes (white arrows): (b) An enlarged lymph node was confirmed before admission. (e) The lymph node had appeared smaller on admission. (h) The lymph node had nearly normalized in size before discharge. The lower panels show the lung tumor in the right lower lobe (black arrow heads): (c) A lung nodule was seen before admission. (f) The lung nodule appeared smaller on admission. (i) The nodule had significantly decreased in diameter before discharge.**

definitive radiotherapy was determined to be difficult to perform due to the extensive disease progression involving the bilateral subclavian lymph nodes. Methotrexate had been discontinued by the time the decision to initiate pembrolizumab immunotherapy was made, as no abnormal joint findings or joint pain had been observed for a long period.

Seven days after the initial pembrolizumab course, bilateral finger and limb joint pain and swelling appeared. The second immunotherapy course was suspended, and prednisolone (10 mg/day) and iguratimod were initiated for the flare-up of rheumatoid arthritis. Although the joint events quickly subsided, the patient became febrile 27 days after pembrolizumab administration and visited our hospital's emergency room on the following day.

A laboratory study revealed decreased blood cell counts, prompting hospital admission. The patient had smoked 20 cigarettes daily for 36 years before he quit smoking at the age of 56. He was a school teacher with no exposure to toxic chemical materials, and his medical history was unremarkable. The patient was administered oral antihypertensive therapy. Although imaging findings of mild interstitial lung disease and emphysema had been observed on

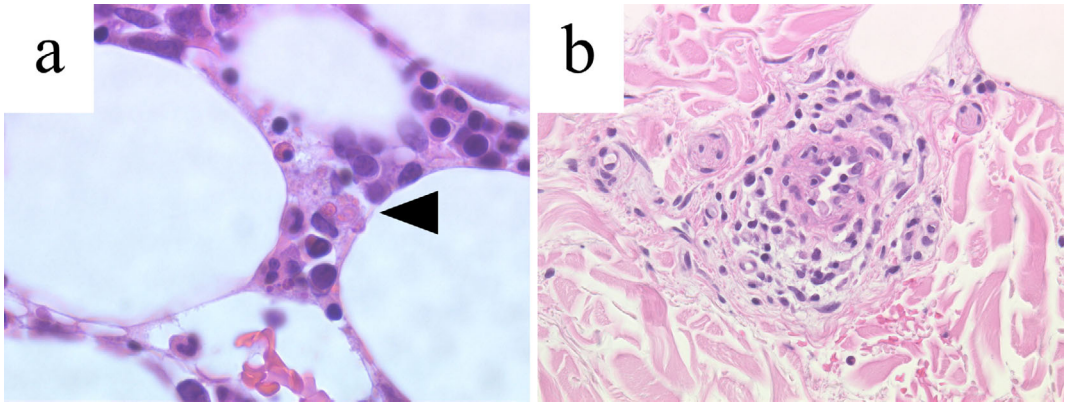

Figure 2. **Biopsy specimen. (a) The bone marrow biopsy, Hematoxylin and Eosin (H&E) staining, 400× magnification. The black arrowhead points to an erythrocyte-phagocytosing macrophage. (b) Perivascular lymphocyte infiltration confirmed by a skin biopsy, H&E staining, 400× magnification.**

CT before the lung cancer diagnosis, these entities were asymptomatic, so no intervention was performed. A medical interview revealed no family history of hematological conditions, connective tissue disorders, or lung cancer. His medication history included prednisolone, iguratimod, olmesartan, amlodipine, celecoxib, and famotidine.

On admission, the patient's temperature was 38.9℃, and his pulse rate was 82 beats per minute. Oxygen saturation was 96% while breathing ambient air. Bilateral basal fine crackles were audible. The patient's liver and spleen were not palpable, and a macular rash was found to have spread over his face, torso, and extremities (Fig. 2). No other skin changes, including skin nodules or mucosal involvement, were observed, and the joint findings had normalized by this point.

A laboratory test results showed a decreased white cell count of 2,710/μL, hemoglobin of 12.0 g/dL, and platelet count of 134,000/μL. An extremely high ferritin level of 28,976 ng/L was detected. The patient's coagulation profile was also abnormal, including a D-dimer level of 156.8 μg/mL. No active viral infection was detected on serology (Table). Blood culture from the sample taken at the emergency room grew no organisms. An electrocardiogram and echocardiography results were unremarkable. CT revealed hepatosplenomegaly. The lung nodule and metastatic lymph nodes were smaller than at the time of the cancer diagnosis (Fig. 1d-f), and a bone marrow biopsy and skin biopsy were planned. The ferritin level and coagulation profile had deteriorated by the next morning, prompting the administration of 1,000 mg of high-dose methylprednisolone and planning of HLH treatment without waiting for the biopsy results. The bone marrow biopsy showed macrophages phagocytosing blood cells and a slightly decreased cellularity. At this point, diagnostic criteria used in the HLH-2004 trial concerning the body temperature, peripheral blood cytopenia, elevated ferritin levels, hemophagocytosis in bone marrow, and hepatosplenomegaly had been met, so an HLH diagnosis was established. The skin biopsy findings were more compatible with drug-induced exanthem than with HLH skin manifestation (Fig. 3).

The patient's clinical course is shown in Fig. 4. Treatment with dexamethasone and etoposide was initiated in accordance with the HLH-94 protocol from the third hospital day. Initial dexamethasone and etoposide doses were 10 mg/m^2 and 150 mg/m^2, respectively. Ferritin levels, which peaked up to 100,000 ng/mL, rapidly fell after HLH-specific treatment initiation, and the blood cell counts also started recovering. Recombinant thrombomodulin was only initially used, as intravascular coagulation was thought to be imminent due to the patient's rapidly deteriorating coagulation profile.

However, on the 9th hospital day, blood cell counts began to fall again. As the ferritin levels were controlled and no other signs of HLH worsening were observed at this point, bone marrow suppression due to etoposide use was suspected, and treatment with this agent was discontinued. The blood cell counts did not recover despite the use of granulocyte colony-stimulating factor, and the patient developed febrile neutropenia on the 15th hospital day. Empirical cefepime was started, and a blood culture grew *Escherichia coli*. Cefepime was subsequently switched to cefmetazole based on sensitivity test results.

The patient responded to antibiotic therapy, and blood cell counts subsequently recovered. As HLH was adequately controlled, dexamethasone was tapered over weeks. CT performed on the 27th hospital day showed a normalized liver and spleen size. The lung tumor and metastatic lymph node diameter had also markedly decreased (Fig. 1g-i). The man was discharged on the 33rd hospital day. At a recent follow-up, he was in complete lung cancer remission without further lung cancer treatment. Disease relapse has not been seen in over seven months.

Discussion

We herein report a case of HLH that developed in a patient with rheumatoid arthritis and advanced lung cancer treated with pembrolizumab. He was successfully rescued by the early initiation of HLH-specific treatment and pembroli-

Table. Laboratory Data on Admission.

White cell count	2,710 /μL	PT	14.2 s
Differential count		APTT	38.9 s
Polymorphonuclear cells	84.8 %	FDP	262.8 μg/mL
Lymphocytes	10.7 %	Fibrinogen	494 mg/dL
Monocytes	3 %	D-dimer	156.8 μg/mL
Basophils	1.1 %	CEA	75.6 ng/mL
Eosinophils	0.4 %	SLX	40 U/mL
Hemoglobin	12.0 g/dL	Rheumatoid factor	236 U/mL
MCV	96.9 fL	Anti-HCV antibody	Negative
Reticulocyte	1.1 %	HBs antigen	Negative
Platelets	134,000 /μL	Anti-HBs antibody	2.0 U/mL
AST	84 U/L	Anti-nuclear antibodies	
ALT	13 U/L	Homogenous pattern	40 ×
LDH	614 U/L	Speckled pattern	40 ×
ALP	199 U/L	MMP-3	113 ng/mL
Total protein	6.2 g/dL	Anti-CCP antibody	387 U/mL
Albumin	2.9 g/dL	IGRA	Negative
Sodium	127 mmol/L	Anti-VZV antibodies	
Potassium	4.4 mmol/L	IgG	12.1 ×
Chloride	95 mmol/L	IgM	0.04 ×
BUN	17 mg/dL	Anti-HSV antibodies	
Creatinin	0.82 mg/dL	IgG	0.8 ×
HDL-C	33 mg/dL	IgM	0.04 ×
LDL-C	79 mg/dL	CMV antigen (C10, C11)	Negative
Triglyceride	88 mg/dL	Anti-EBV antibodies	
Hemoglobin A1c	5.8 %	IgG	160 ×
Haptoglobin	236.0 mg/dL	VCA-IgM	Negative
CRP	8.05 mg/dL	EA-DR-IgG	Negative
sIL-2R	4,625 U/mL	EBNA-IgG	80 ×
Iron	44 μg/dL	Anti-HHV-6 antibodies	
TIBC	217 μg/dL	IgG	80 ×
Ferritin	28,976 ng/mL	IgM	Negative

ALT: alanine aminotransferase, ALP: alkaline phosphatase, APTT: activated partial thromboplastin time, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CCP: cyclic citrullinated protein, CEA: carcinoembryonic antigen, CMV: cytomegalovirus, CRP: C-reactive protein, EBV: Epstein-Barr virus, FDP: fibrin degradation products, HBs: hepatitis B surface, HCV: hepatitis C virus, HDL-C: high density lipoprotein cholesterol, HHV-6: human herpesvirus-6, HSV: herpes simplex virus, IGRA: interferon-gamma release assay, LDH: lactate dehydrogenase, LDL-C: low density lipoprotein cholesterol, MCV: mean corpuscular volume, MMP-3: matrix metalloprotease-3, PT: prothrombin time, sIL-2R: soluble interleukin-2 receptor, SLX: sialyl SSEA-1, TIBC: total iron binding capacity, VZV: varicella-zoster virus

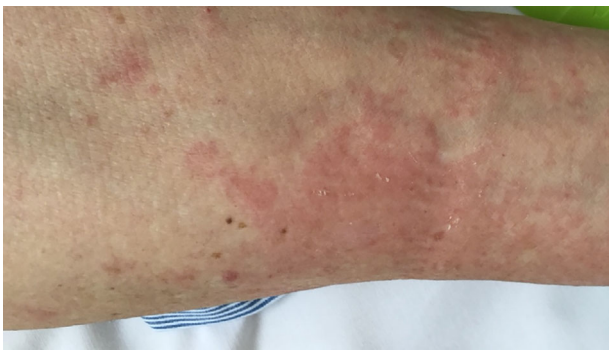

Figure 3. Physical findings. Macular rash observed on the forearm.

zumab discontinuation.

Adult-onset HLH is triggered by immune-activating events, such as infection or treatment initiation, in patients with coexisting morbidity. Accurately identifying the HLH trigger is relevant. Familial HLH was unlikely in the present case, as it almost invariably occurs in children, and adult-onset familial HLH is extremely rare in patients over 60 years old (3). No attributable active infection was observed in this case. Hematological malignancy is one of the common underlying conditions, with solid tumors only accounting for 3.1% of cases in a systematic review of malignancy-associated HLH. Even when a malignancy is underlying HLH development, it is not usually the trigger itself (4). In the present case, the rheumatoid arthritis flare-up episode may have been the HLH trigger. However, the root cause of HLH development in this case is thought to be due to the initiation of lung cancer treatment, as both methotrexate discontinuation and pembrolizumab administration preceded the

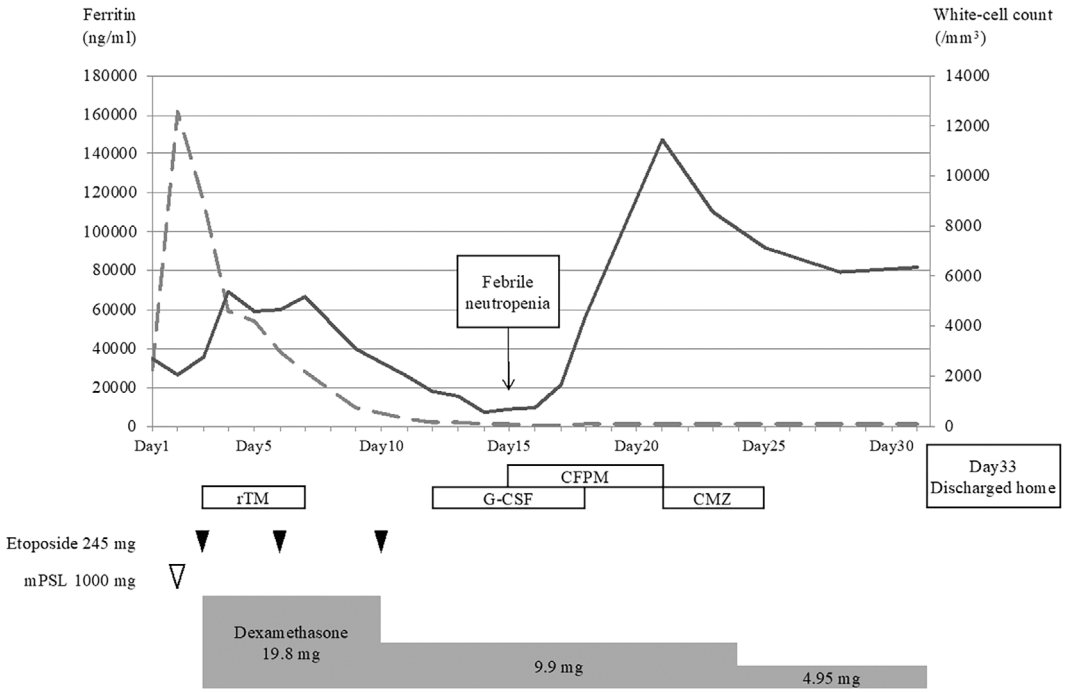

Figure 4. **The patient's clinical course. Continuous and dashed lines indicate the white cell counts and ferritin levels, respectively. The patient developed febrile neutropenia on the 15th hospital day and was discharged on the 33rd hospital day. CFPM: cefepime, CMZ: cefmetazole, G-CSF: granulocyte colony-stimulating factor, mPSL: methylprednisolone, rTM: recombinant thrombomodulin**

arthritis flare-up and HLH development.

Whether to continue or discontinue immunosuppressive agents before and during ICI treatment in a patient with a pre-existing autoimmune disease is controversial. It has been reported that irAEs are more frequent in this group of patients and that a considerably large proportion of patients experience flare-ups of their pre-existing conditions during immunotherapy (5). IrAEs or flare-ups in patients with autoimmune diseases are rarely severe enough to require permanent immunotherapy discontinuation (6, 7). In the present case, methotrexate was stopped before pembrolizumab initiation for two reasons: good disease control without noticeable rheumatoid arthritis flare-ups had been observed, and methotrexate persistence would have put the patient at an increased risk of fatal pulmonary injury. He had multiple reported risk factors of methotrexate-induced lung disease, including an advanced age and pre-existing lung disease (8, 9). These risk factors seem to overlap with those of immune checkpoint inhibitor-related pneumonitis (10). We chose to discontinue methotrexate in an attempt to reduce the patient's risk of developing fatal pneumonitis, but methotrexate discontinuation may have led to the patient's ultimate condition. However, methotrexate discontinuation alone cannot entirely explain HLH development, since rheumatoid arthritis is an uncommon autoimmune disorder associated with HLH, and common triggers in patients with connective tissue diseases include infection and immunosuppressive agents, such as infliximab (11).

The present case seems to have involved an ICI-associated event. Although HLH association with advanced malignancies has been described, it is not yet acknowledged as a severe adverse event following ICI administration. To our knowledge, there have only been three previous reports on ICI-related HLH. Two of them involved melanoma and bladder cancer (12, 13). The other one referred to a lung cancer patient on pembrolizumab without rheumatologic conditions (14). In the literature, PD-L1 inhibitors have long been described in the context of their T-cell activating effects. Recent studies have also revealed their driving effects on macrophages (15), the excessive activation of which is an essential mechanism in HLH pathogenesis (16, 17). These clinical reports, in addition to our experience and basic science study results, support the theoretical induction of HLH by overly activated macrophages due to PD-L1 inhibitors. In the present case, based on this scientific body of knowledge and the fact that no other events were equally responsible, the HLH trigger can reasonably be attributed to pembrolizumab.

The HLH prognosis varies and partly depends on the patient background. Idiopathic HLH associated with congenital gene mutations has a poor prognosis (18), while HLH with an obvious modifiable underlying condition, such as rheumatic diseases, has a better prognosis. Regarding ICI efficacy in cases of lung cancer, studies in melanoma and non-small-cell lung cancer have reported that patients experiencing irAEs with ICIs have better survival outcomes than those who do not (19, 20). Despite its fulminant nature, ICI-triggered HLH can be reversible, and the patient may actually benefit from the unprecedented cancer treatment strategy of ICIs. Therefore, awareness of the condition and early

treatment institution are important.

In conclusion, we herein report a case of pembrolizumab-induced HLH in a patient with rheumatoid arthritis. The patient survived and remains in complete cancer remission. While ICIs have shown significant efficacy, potentially fatal adverse events may follow. A high degree of suspicion and early intervention are important in order to ensure favorable patient outcomes.

The authors state that they have no Conflict of Interest (COI).

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