A case of pembrolizumab-induced hemophagocytic lymphohistiocytosis successfully treated with pulse glucocorticoid therapy

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ABSTRACT

Treatments using immune checkpoint inhibitors such as pembrolizumab lead to immune mediated adverse effects including hemophagocytic lymphohistiocytosis (HLH). Herein, we present a case where HLH developed after pembrolizumab administration, which was treated using high dose prednisolone. He developed high-grade fever complicated with liver dysfunction and diarrhea 7 days after pembrolizumab administration. Although treatment with oral prednisolone alleviated the symptoms, other adverse effects arose owing to a tapered prednisolone dose. Hyperferritinemia suggested the diagnosis of HLH and met the criteria for HLH. He was thus administered intravenous pulses of methylprednisolone followed by high-dose oral prednisolone, which resolved these symptoms.

1. Introduction

Immune checkpoint inhibitors (ICIs) are being increasingly used to treat cancers in various organs and have achieved remarkable clinical benefits. Pembrolizumab is an immune checkpoint inhibitor that exerts antitumoral activity by targeting programmed cell death protein 1 (PD-1). However, immune checkpoint inhibitors including pembrolizumab activate T-cells and induce severe autoimmune complications, known as immune-related adverse events (irAEs), affecting almost all organ systems. Hemophagocytic lymphohistiocytosis (HLH) is a potentially fatal disorder, which needs immediate treatment, is often underdiagnosed, and is characterized by fever, skin rashes, cytopenia, liver dysfunction and the presence of hemophagocytic activity in the bone marrow. Recently, HLH that were triggered by immune checkpoint inhibitors have been reported in single case reports [1–6]. The single use of glucocorticoids had been thought effective for this immune-related adverse events [4,5], but the latest recommendations mention that HLH with organ toxicities ≥ grade 3 should be managed with glucocorticoids and anti–IL-6 therapy, and additional therapy with etoposide for intractable cases [7].

Here, we report the case of a patient with advanced non-small cell lung cancer treated using pembrolizumab, who developed HLH and was successfully treated with pulse therapy using high-dose glucocorticoids.

2. Case report

A 78-year-old man with a 20-pack-year smoking history visited our hospital with dyspnea. He was admitted and his chest X-ray showed massive right pleural effusion. PET/CT and MRI scans revealed right pleural effusion with a right lower lobe tumor with pleural thickening, metastasis to the right adrenal gland and liver, with no evidence of brain metastasis (Fig. 1). Tumor cells detected in the pleural effusion showed morphological features of adenocarcinoma, were negative for driver mutations and showed PD-L1 expression in >50% of the cells. The histological specimen was not available. He was diagnosed with advanced lung adenocarcinoma and was classified as Stage cT3N3M1b. Talc pleurodesis was performed, followed by administration of 2 cycles of chemotherapy with carboplatin and pemetrexed.

Unfortunately, he had developed Grade 3 bacterial pleurisy after 2 cycles of chemotherapy, which made him discontinue the platinum-based doublets chemotherapy even after he got cured. Three weeks later, he was admitted again as he required treatment with pembrolizumab (200 mg/kg, every 3 weeks) as a second-line drug.

His blood picture showed mild microcytic anemia, with normal hepatic and renal functions and was negative for serum antinuclear antibodies (Table 1). His performance status (PS) was 1 as per the Eastern Cooperative Oncology Group (ECOG) score. He received pembrolizumab intravenously (200 mg/kg) and 7 days after the first dose, he developed a high-grade fever followed by diarrhea.
with elevated liver enzymes (Fig. 2).

He was suspected to have immune-mediated hepatitis and was treated with 40 mg of prednisolone daily and antibiotics (liver biopsy was not performed), and pembrolizumab administration was discontinued. Although these symptoms improved gradually and prednisolone was tapered to 30 mg within 6 weeks, the patient developed symptoms of fever, skin rashes, cytopenia and liver dysfunction. Laboratory examination revealed thrombocytopenia, hypofibrinogenemia, elevated ferritin, liver enzyme levels and serum soluble interleukin-2 receptor (IL-2R), but all screening tests for viruses were negative (Table 1).

A bone marrow aspiration showed a normoblastic marrow with hemophagocytic macrophages without metastatic tumor cells or lymphocytic infiltration (Fig. 3).

Thus, this case met at least five out of the following eight diagnostic criteria for HLH described in HLH-2004 [8]: fever, hypertriglyceridemia/hypofibrinogenemia (≥150 mg/dL), elevated ferritin (≥500 gm/mL), hemophagocytosis in bone marrow/spleen/lymph nodes, cytopenias and elevated soluble CD25 (ie, IL-2R) ≥2400 U/mL; Cytopenias, splenomegaly or low or absent natural killer (NK)-cell activity were uncertain.

He was administered intravenous methylprednisolone (1000 mg/day for 3 days) for the treatment of irAEs 46 days after the first dose of pembrolizumab. This steroid pulse therapy rapidly alleviated fever, rashes, and abnormal laboratory values.

After the pulse steroid therapy, he received 60 mg/day (1 mg/kg/day) of prednisolone, which was tapered to 50 mg/day within 4 weeks without recurrence of symptoms, following which he was discharged.

The lung tumor showed complete response by CT for about 3 months, after which best supportive care alone was provided as new metastases developed.

### 3. Discussion

Recent retrospective observational cross-sectional studies have shown that the incidence of immune checkpoint inhibitors-related HLH was estimated to be < 0.1%, which was resolved in 61% of cases with the use of steroids; however, the dosage of steroids is not reported [9].

In this case, the high-grade fever and elevation of liver enzymes preceding cytopenia were first assumed to be immune-related hepatitis,
but were in fact the peripheral symptoms of HLH. This assumption was due to the increasing incidence of HLH as an immune related adverse effect [9].

Thus, HLH should be suspected when a patient on immune checkpoint inhibitors develops symptoms such as fever, skin rashes, cytopenia, or liver dysfunction [4]; however, these are non-specific clinical features and may mimic other irAEs, hepatitis or sepsis-like clinical presentation. We could distinguish these differential diagnosis in the deteriorating state by elevated ferritin, which is important screening marker for HLH [10].

ICIs can trigger uncontrolled activation of T-cells, causing hypersecretion of cytokines; corticosteroids and etoposide can resolve both activated T-cells and inflammatory cytokine production. A notable point in this case is that the patient developed HLH despite having received mid-dose prednisolone maintenance therapy. Hence, it was inferred that the dosage of 30 mg of prednisolone is not enough to control the autoimmune complications, and high dose pulse steroid therapy is required. We had considered next using etoposide if the patient had no serological improvement [7].

Although immune checkpoint inhibitor-related HLH can lead to progressive tissue damage, organ failure, and possibly death, early diagnosis and treatment is essential for them [4]. As demonstrated in this case, the steroid pulse therapy rapidly alleviated symptoms of HLH. Many case reports are available on ICI induced HLH patients who were successfully treated with high-dose glucocorticoids (Table 2).
However, these case reports do not indicate the required dosage of glucocorticoids.

In this report, we infer that mid-dose steroids cannot effectively control these immune related adverse effects.

4. Conclusion

In conclusion, a patient with advanced non-small cell lung cancer developed HLH as a complication of pembrolizumab therapy, which was then successfully treated with high-dose glucocorticoids. Clinicians should be aware of ICI-related HLH, as it is potentially fatal. In addition, symptoms of fever and skin rashes, along with laboratory findings such as thrombocytopenia and liver dysfunction may mimic other immune related adverse effects, hepatitis, or sepsis-like clinical presentation. In such cases, ferritin is important marker for HLH to distinguish them; early treatment is also essential for this life threatening irAE.

We recommend high-dose pulse glucocorticoid for the treatment of ICI-related HLH. The appropriate dosage and use of immunosuppressive agents for managing immune related adverse events, however, still require further research.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101097.

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