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Letter to the Editor

Secondary haemophagocytic lymphohistiocytosis due to checkpoint inhibitor therapy

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To the Editor,

We present a patient with metastatic melanoma who developed haemophagocytic lymphohistiocytosis (HLH) following combination checkpoint inhibitor (CI) therapy who responded to single-agent steroid therapy, and we present a brief literature review on this topic. HLH is a life-threatening disorder characterised by uncontrolled immune activation and cytokine-mediated proliferation of macrophages with multisystem involvement and consequences. HLH can be due to inactivating mutations in cytotoxic T and/or natural killer (NK) cells or secondary to a wide range of systemic disorders including systemic lupus erythematosus, Epstein–Barr virus infection, metastatic solid organ tumours and T-cell lymphoproliferative disorders. Immunotherapies emerging in the field of cancer therapy can cause a spectrum of autoimmune complications, although rare, numerous case reports have described HLH with the use of CIs [1–4]. Single-agent corticosteroid therapy has been shown to be highly effective with minimal toxicity in the management of CI-related HLH.

A 69-year-old woman with metastatic melanoma presented with a 3-week history of persistent fevers, lethargy, abdominal distension and swelling. She previously received four cycles of ipilimumab and nivolumab with a near complete response and continued fortnightly on nivolumab with the last dose a month before presentation. Examination revealed fever (38.6°c) with palpable hepatosplenomegaly. Abdominal distension was present with bilateral pitting oedema. Investigations revealed anaemia, thrombocytopenia, hyponatraemia, hyperferritinemia (119000 ug/L [30–300 ug/L]), hypofibrinogenaemia and hypertriglyceridaemia. Blood film showed no evidence of haemolysis, red cell fragments, platelet anisocytosis or blast cells. Computerised tomography imaging showed no evidence of progressive metastatic disease. Bone marrow aspirate and trephine were performed which showed florid histiocytosis and haemophagocytosis (Fig. 1) without evidence of metastatic infiltration. Soluble CD25 levels were elevated with reduced functional NK cell activity.

These findings were consistent with a diagnosis of HLH, fulfilling all eight diagnostic criteria. CI therapy was discontinued. Intravenous methylprednisolone was

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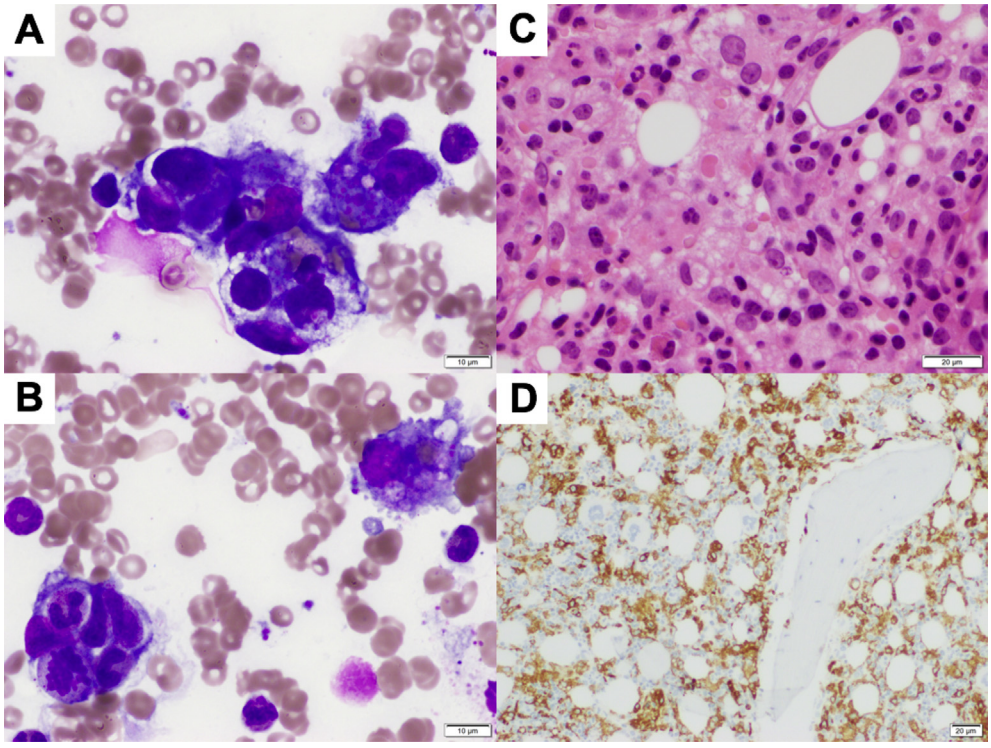

Fig. 1. (A and B) Bone marrow aspirate showing florid histiocytosis with haemophagocytosis, (C) bone marrow trephine infiltrated with histiocytes with haemophagocytosis present and (D) CD163 highlighting increased numbers of histiocytes in the bone marrow trephine.

administered for three days (1500 mg daily), followed by oral prednisolone 1 mg/kg/day tapered over two months. Over a period of six weeks, the haemophagocytic syndrome rapidly improved with normalisation of ferritin, fibrinogen and cytopenia. At one month from discontinuation of steroid therapy, she remains in remission from HLH. The metastatic melanoma remains stable with slow progression. When there is clinical need, we would consider rechallenge with checkpoint inhibition under close observation, given her initial response and the lack of therapeutic options.

CIs inhibit transmembrane proteins including programmed cell death 1 (PD-1), PD-1 ligand, PD-2 ligand and cytotoxic T-lymphocyte–associated antigen 4 to promote apoptosis of tumour cells and induce a peripheral T-cell response. Combination checkpoint blockage strategies have demonstrated significantly higher response rates compared with monotherapy in metastatic melanoma. CIs commonly cause immune-related adverse events (irAEs) such as colitis, dermatitis, pneumonitis and hepatitis. Severe irAEs related to CI therapy including autoimmune haemolytic anaemia, pure red cell aplasia and HLH have been described [5].

The timing of CI-related HLH varies widely, ranging from 5 days to 17 months, following initiation of therapy [1–5]. Approaches to treatment of HLH are heterogenous (Table 1). Single-agent corticosteroid therapy has been successfully used in four other cases of CI-related HLH across a range of malignancies with good tolerability [3–6]. In two cases, mycophenolate mofetil or etoposide in conjunction with corticosteroids effected complete resolution of HLH [1, 2]. Other available options include tocilizumab, cyclosporine or intravenous immunoglobulin. In the described cases, the haemophagocytic syndrome rapidly resolved within two months of corticosteroid therapy. CI therapy was permanently discontinued in all patients. In this limited case series, the outcomes of CI-related HLH appear favourable compared with HLH secondary to other causes.

Given CIs are used in the relapsed/refractory setting, the outcomes without further immunotherapy are dismal. A review of 80 patients rechallenged with CI therapy (discontinued because of previous irAE) identified 14 patients (18%) with recurrent irAEs at a median of 14 days after therapy resumption (7 patients with grade 3 or 4 toxicity) [7]. The duration of steroid taper, severity of initial irAEs and use of additional immunosuppressants did not predict toxicity on rechallenge. Patients with severe irAEs such as HLH were not included. Further observational studies are required to assess the safety of rechallenging patients with severe irAEs such as HLH with CIs.

In summary, HLH is a rare and life-threatening irAE associated with CI therapy. Treatment discontinuation and high-dose corticosteroids may be sufficient to control HLH. The outcomes of CI-related HLH appear favourable when compared with other causes. There

Table 1
Summary of case reports of haemophagocytic lymphohistiocytosis (HLH) secondary to checkpoint inhibitor therapy.

Case	Clinical and laboratory findings	Treatment	Outcome
Hantel *et al.* [5]			
35 F with metastatic melanoma. Ipilimumab and nivolumab 3 weeks before presentation.	Splenomegaly, anaemia, thrombocytopenia, hyperferritinemia, hypertriglyceridaemia, raised soluble CD25. BMAT showed haemophagocytosis with histiocytosis, MF-2 fibrosis.	1.5 mg/kg i.v. methylprednisolone q8h for 4 days, then 1 mg/kg PO prednisolone for 1 month. Slow taper of PO prednisolone dose thereafter.	Complete remission after 2 months of steroid therapy. Remains off treatment and in complete remission 12 months later.
Malissen *et al.* [3]			
77 M with metastatic melanoma. Nivolumab for 17 months with ongoing partial response.	Fever, bicytopenia, hyperferritinemia, haemophagocytosis on BMAT, raised NK cell activity.	0.5 mg/kg steroids followed by PO prednisolone daily for 6 weeks.	Died 6 weeks following diagnosis from concurrent fungal bronchopneumopathy.
42 M with metastatic melanoma. Nivolumab for 9 months, ceased 3 months ago because of gastrointestinal progression. Ipilimumab for 5 days before presentation.	Fever, hepatomegaly, bicytopenia, hyperferritinemia, hypertriglyceridaemia. No haemophagocytosis on BMAT.	Systemic corticosteroid therapy and antibiotic therapy (amoxycillin, clavulanic acid, vancomycin) for *Staphylococcus epidermidis* bacteraemia	Complete remission.
81 M with Merkel cell carcinoma. Treated with avelumab as second-line therapy, presented at day 5 following first infusion.	Fever, hepatomegaly, bicytopenia, hypertriglyceridaemia, hyperferritinemia. BMAT not performed.	High-dose steroid therapy	Died rapidly despite introduction of high-dose steroids.
Sadaat and Jang [6]			
58 M with metastatic melanoma. Presented 31 days after receiving 6 doses of pembrolizumab.	Fever, arthralgias, bicytopenia, hypertriglyceridaemia, hyperferritinemia, splenomegaly. No BMAT performed.	1 mg/kg PO prednisolone for 5 weeks, then tapered over 7 weeks.	Complete remission after 12 weeks of therapy. Pembrolizumab permanently discontinued. Remission from metastatic melanoma for 1 year before progressing.
Satzger *et al.* [2]			
26 M with metastatic melanoma. Presented one week after the fourth cycle of nivolumab and ipilimumab.	Fever, liver enzyme abnormalities, increased soluble CD25, pancytopenia, hyperferritinemia, hypofibrinogenaemia, haemophagocytosis on liver biopsy.	2 mg/kg PO prednisolone for 7 days, then tapered to 1.5 mg/kg/day + MMF 360 mg BD, then 1 mg/kg/day + MMF 720 mg BD	Complete remission. Remission from metastatic melanoma. Nivolumab and ipilimumab permanently discontinued.
Shah *et al.* [1]			
76 M with metastatic bladder cancer. Pembrolizumab for 9 months before presentation.	Fever, splenomegaly, rash, pancytopenia, hyperferritinemia, hypofibrinogenaemia, reduced NK cell activity, BMAT showed haemophagocytosis with histiocytosis.	HLH 2004 protocol − Dexamethasone and etoposide IV	Outcome unknown
Takeshita *et al.* [4]			
63 F with squamous non−small cell lung cancer (NSCLC). Two doses of nivolumab, presented 25 days after nivolumab initiation.	Fever, pancytopenia, hyperferritinemia, pneumonitis, BMAT showed haemophagocytosis with histiocytosis, Stevens−Johnson syndrome.	i.v. methylprednisolone 1000 mg/day for 3 days, then 500 mg/day for 3 days, then 250 mg/day for 3 days, then transitioned over to PO prednisolone 0.5 mg/kg/day	Complete remission. Partial response of squamous NSCLC 2 months after last nivolumab treatment. Not rechallenged.

BMAT, bone marrow aspirate and trephine; PO, oral; NK, natural killer; MMF, mycophenolate mofetil, i.v., intravenous; F, female; M, male; q8h = eight hourly; BD = twice daily.

exists a paucity of outcome evidence in rechallenging patients with severe irAEs such as HLH with CI therapy.

Authorship contributions

C.K.C., S.H., C.G., G.V.H., D.S. and C.Y.C. wrote the manuscript. S.H. created the figures.

Conflict of interest statement

No conflicts of interest to declare from all authors.

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