Haemophagocytic lymphohistiocytosis as a complication of combination anti-PD-1 and anti-CTLA-4 checkpoint inhibitor immunotherapy for metastatic melanoma, and the outcome of rechallenge with single-agent anti-PD-1 immunotherapy

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SUMMARY

A woman with metastatic melanoma was treated with ipilimumab and nivolumab and radiotherapy to liver metastases. The patient deteriorated shortly thereafter, becoming febrile and hypotensive and requiring admission to the intensive care unit (ICU) for inotrope support. Failure to respond to antibiotics and a negative septic screen prompted further investigation, which ultimately led to a diagnosis of haemophagocytic lymphohistiocytosis (HLH). The patient improved on high dose steroids and was discharged home. Months later, in the context of progressive melanoma, the patient was re-challenged with nivolumab monotherapy and subsequently experienced recurrence of HLH, confirming the aetiology as being immunotherapy related. This case serves as a reminder to consider HLH where there are fevers of unknown origin in an unwell patient receiving immune checkpoint inhibitor therapy and also highlights immunotherapy as a potential cause for HLH, which has rarely been reported in the literature to date.

BACKGROUND

Recent advances in the use of immunotherapy have revolutionised the treatment of many cancers, including melanoma. Within the past decade, immune checkpoint inhibitors (ICIs) targeting programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have been demonstrated to significantly prolong overall survival and produce durable responses in patients with metastatic melanoma.[1] However, due to the manner by which these drugs work by up-regulating the immune system, they have the potential to cause serious immune-related adverse events (irAE).[1]

Haemophagocytic lymphohistiocytosis is a rare and aggressive syndrome of excessive immune activation that is thought to result from the absence of normal downregulation driven by activated macrophages and lymphocytes.[2] It is primarily a paediatric illness, with an estimated incidence of 1.2 cases per million children each year, but it is also known to affect adults.[3] In adults, it is often associated with triggers such as infection, malignancy and rheumatological disorders. Clinical features include fever, organomegaly, cytopenias, elevated ferritin, elevated lactate dehydrogenase (LDH) and haemophagocytosis on bone marrow aspirate.[4] The diagnostic criteria from the HLH-2004 guidelines are commonly used to help confirm a diagnosis of HLH. Management involves addressing the underlying cause in addition to the use of corticosteroids and chemotherapeutic agents such as etoposide. However, even with best available treatment, the prognosis is poor, with only a 55% chance of survival.[3]

To date, there have been very few cases reported of ICIs causing HLH.[4–10] Additionally, data relating to outcomes of ICI rechallenge after an index episode of HLH are even scarcer.

CASE PRESENTATION

A woman in her 40s presented with a 1-month history of malaise, nausea, vomiting, fatigue, anorexia and 14 kg of unintentional weight loss on a background of a right shoulder melanoma excision in 1995.

Her medical history was otherwise significant for coeliac disease, which was well controlled with a gluten-free diet. She previously smoked from age 16 to 30 and infrequently drank alcohol. There was no known relevant family history.

CT showed innumerable metastases in the liver, as well as metastases to bone and spleen. MRI of the brain was unremarkable. Subsequent positron emission tomography (PET) showed extensive fluorodeoxyglucose-avid (FDG) metastatic disease involving the liver, spleen, lung, skeleton and lymph nodes, consistent with stage IV melanoma (see figure 1). Liver biopsy confirmed BRAF V600E mutant-positive metastatic melanoma.

Due to the high volume of disease and the desire to achieve prompt tumour debulking, she was given a 2 week course of dabrafenib upfront, before receiving her first cycle of combination immunotherapy in the form of ipilimumab 3 mg/kg and nivolumab 1 mg/kg. Additionally, because of her particularly heavy burden of liver metastases causing significant symptoms, she was offered palliative radiotherapy to the liver, at a dose of 12 grey in four fractions. Two weeks after her first dose of immunotherapy, on the same day of receiving first fraction of radiotherapy to liver mets, the patient deteriorated, becoming febrile and hypotensive requiring an admission to the intensive care unit