EJCRIM
European Journal
of Case Reports
in Internal Medicine

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS FOLLOWING THE ANTI-PD-1 NIVOLUMAB IN A PATIENT WITH GASTRIC CANCER AND ANKYLOSING SPONDYLITIS

Clara Long[1*], Abdulrahman Al-Abdulmalek[1*], Jonathan Lai[2], David G. Haegert[2], Stephane Isnard[3,4], Denis Cournoyer[1,5,6], Jean-Pierre Routy[1,3,4,5,6]

[1] Department of Medicine, McGill University Health Centre, Montreal, Canada
[2] Department of Pathology, McGill University Health Centre, Montreal, Canada
[3] Research Institute of the McGill University Health Centre, Montreal, Canada
[4] Chronic Viral Illness Service, McGill University Health Centre, Montreal, Canada
[5] Department of Medicine and Oncology, McGill University, Montreal, Canada
[6] Division of Hematology, McGill University Health Centre, Montreal, Canada
[*] Contributed equally

Corresponding author: Jean-Pierre Routy **e-mail:** jean-pierre.routy@mcgill.ca

Received: 09/02/2024 **Accepted:** 27/02/2024 **Published:** 28/03/2024

Conflicts of Interests: The Authors declare that there are no competing interests.
Patient Consent: Signed consent has been obtained from the patient.
Acknowledgements: The authors are grateful to the nursing and administrative staff of the McGill University Health Centre including Ms. Angie Massicotte for coordination and assistance.

How to cite this article: Long C, Al-Abdulmalek A, Lai J, Haegert DG, Isnard S, Cournoyer D, Routy JP. Haemophagocytic lymphohistiocytosis following the anti-pd-1 nivolumab in a patient with gastric cancer and ankylosing spondylitis. *EJCRIM* 2024;**11**:doi:10.12890/2024_004370.

ABSTRACT

Background: Autoimmune diseases are not contraindications for immune checkpoint inhibitors (ICI) therapy in patients with cancer. However, immune-related adverse events (irAEs) are frequently observed in patients receiving ICIs including dermatitis, thyroiditis, colitis, and pneumonitis. Thrombocytopenic purpura, aplasia, and haemophagocytic lymphohistiocytosis (HLH) are rarely observed during ICIs.

Case description: We report the case of a male patient with pre-existing untreated HLA B27 and ankylosing spondylitis with gastric cancer and liver metastases. The 79-year-old man was treated with anti-HER2 trastuzumab and anti-PD-1 nivolumab. Seventeen days after the seventh cycle of treatment, he presented at the emergency department with acute fever, confusion, and hypotension. Laboratory results showed pancytopenia, and elevation of ferritin and triglyceride. No infections were detected. Although not seen in a bone marrow biopsy, clinical presentation, and absence of infection, together with an H-score of 263, indicated HLH. The patient was treated with dexamethasone for four days and discharged on a tapering dose of steroids. At the two-month follow-up, clinical presentation was normal and blood test almost normalised. At 8 months, no liver metastases were observed.

Conclusions: In a patient with a pre-existing autoimmune condition, immunotherapy led to the development of HLH, which was controlled by glucocorticoid. Absence of the feature of haemophagocytosis in the bone marrow biopsy did not exclude the diagnosis, as HLH can occur in the spleen or in the liver. Glucocorticoid therapy did not prevent the anti-cancer effect of ICIs, and liver metastases disappeared 8 months post-HLH. This case warrants further research on the interplay between autoimmunity and ICI response, as well as ICI-induced irAEs.

KEYWORDS

Haemophagocytic lymphohistiocytosis, immunotherapy, anti-PD1, gastric cancer, ankylosing spondylitis

EFIM
European Federation of Internal Medicine

Publisher
smc media srl

LEARNING POINTS

- Haemophagocytic lymphohistiocytosis (HLH) post seventh cycle of trastuzumab (anti-HER2) and nivolumab (anti-PD-1) was controlled with glucocorticoid.
- Breach of tolerance was due to immunotherapy-induced HLH in a patient with pre-existing autoimmune condition (HLA B27- positive ankylosing spondylitis).
- There was a complete disappearance of liver metastases 8 months post-HLH.

INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a rare and potentially fatal condition of immune hyperactivation. While primary HLH results from mutations related to cytotoxic pathways, secondary HLH can be triggered by malignancies, autoimmune diseases and medications including ICIs. The enhancement of immune responses upon ICIs treatment can reinvigorate anti-tumour immune surveillance, sometimes at the cost of immune-related adverse events (irAEs), which frequently include dermatitis, thyroiditis, colitis, pneumonitis, and rarely immune thrombocytopenic purpura, aplasia and HLH. In absence of identified factors contributing to the development or protection against irAEs, their morbidity remain important[1].

CASE DESCRIPTION

A 79-year-old male presented with stage 4 gastric adenocarcinoma with liver metastasis positive for human epidermal growth factor receptor 2 (HER2). He was treated with subtotal gastrectomy and adjuvant immunotherapy including trastuzumab, a humanised anti-HER2 monoclonal antibody, and nivolumab, an anti-PD-1 monoclonal antibody. His past medical history was remarkable for untreated ankylosing spondylitis being positive for HLA B27 and Paget's disease. Initially, cycles of immunotherapies were well tolerated and led to the disappearance of liver metastasis. However, he presented at the emergency room 17 days post his seventh cycle of trastuzumab and nivolumab therapy, with acute fever up to 39.3°C, heart rate at 78/min, blood pressure 120/70, respiratory rate of 20 breaths/min and saturation at 98%. Although confused, the patient was cooperative and calm. The physician examination did not identify possible sources of infection and no abdominal mass, enlarged lymph node or hepatosplenomegaly were observed. Laboratory findings (summarised in *Table 1*) revealed a new onset of pancytopenia with high neutrophils, lymphocytes, haemoglobin, and platelets. The ferritin level was extremely elevated at 57,962 µg/l, triglyceride (TG) at 3.4 mmol/l, lactate dehydrogenase (LDH) at 2,756 U/l and C-reactive protein (CRP) at 162 mg/l. Fibrinogen levels were low. Liver function test showed elevated aspartate and alanine aminotransferase (AST and ALT). Blood, urine, and sputum cultures were all negative as well as COVID-19, HIV and viral hepatitis B and C tests. Epstein Barr virus DNA was detected in the blood at 1,023 copies/ml. Cytomegalovirus DNA levels were below level of detection.

The combination of acute onset of fever post ICIs and pancytopenia with extreme elevation of ferritin, LDH and TG in the absence of COVID-19 suggested HLH. A bone marrow biopsy was performed and revealed an aplastic bone marrow without definite evidence of haemophagocytosis or infiltration from malignancy *(Fig. 1)*. The H-score was calculated at 263. The H-score, which encompasses common clinical criteria (known immunosuppression, high temperature, organomegaly), laboratory results (triglyceride, ferritin, serum glutamic oxaloacetic transaminase, fibrinogen, cytopenia) and one cytologic parameter (haemophagocytosis features on bone marrow aspirate) are commonly used to assess HLH diagnosis[2]. A score greater than 250, together with clinical presentation in the absence of detected infection strongly indicated HLH; trastuzumab was then withheld.

The patient was treated with dexamethasone 40 mg daily for 4 days with a significant clinical improvement. After three weeks, his ferritin levels normalised at 175, triglyceride at 0.96 mmol/l and CRP at 0.7 mg/l. The blood counts showed 3.8 × 10^9/l neutrophils, haemoglobin of 94 g/l and platelets at 109 × 10^9/l. He was discharged on a tapering dose of steroids. On a 2-month follow-up, the patient continued to demonstrate improvement *(Table 1)*. At 8 months, the patient presented no HLH signs.

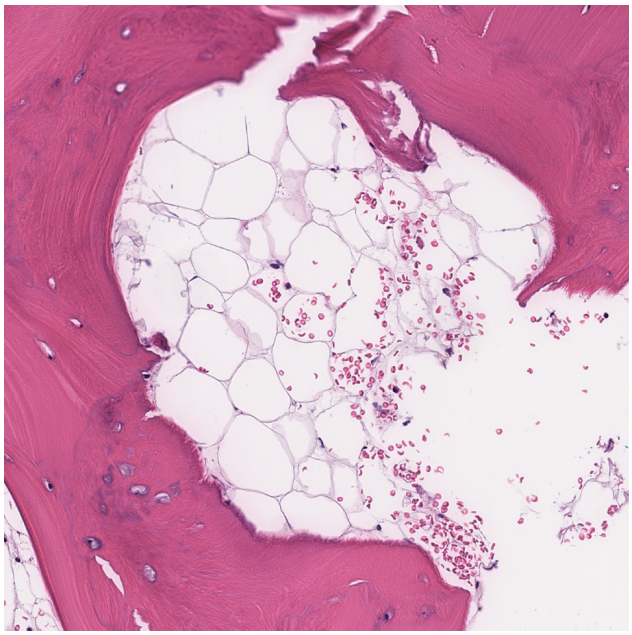

Figure 1. Bone marrow biopsy: Essentially acellular/aplastic marrow with no definite haematopoiesis identified.

Variable	Reference Range*	At presentation	On discharge	2-month follow-up	8-month follow-up
Haemoglobin (g/l)	140–175	85	73	104	135
Haematocrit (%)	42–50	27	22	32	40
Mean corpuscular vol-ume (fl)	80–96	66.1	74.5	79.6	89.8
Platelet count (×10⁹/l)	150–400	48	176	214	174
White blood cells (×10⁹/l)	4–11	1.7	2.7	3.2	3.8
Neutrophils (×10⁹/l)	1.8–7.5	0.76	1.89	1.89	2.76
Lymphocytes (×10⁹/l)	1.2–3.5	0.9	0.56	0.8	0.78
Monocytes (×10⁹/l)	0.2–0.8	0.7	0.2	0.32	0.28
Eosinophils (×10⁹/l)	0–0.5	0	0	0.14	0.02
Basophils (×10⁹/l)	0–0.2	0.01	0	0.03	0.01
Total Bilirubin (µmol/l)	1.7–18.9	16.1	21.3	6.7	14.4
ALT (U/l)	6–45	43	36	10	10
AST (U/l)	6–35	196	34	15	13
ALP (U/l)	56–120	50	54	52	45
Na (mmol/l)	133–143	132	139	129	143
K (mmol/l)	3.5–5	3.5	4.3	3.9	4.5
HCO3 (mmol/l)	23–29	27	27	27	31
Creatinine (µmol/l)	55–110	82	77	63	74
Lactate dehydrogenase (U/l)	110–220	2,756	611	159	117
C-reactive protein (mg/l)	0–10	162.3	18.8	0.5	0.4
Prothrombin time (s)	9.4–12.9	16.3	16.4	15.5	15.6
Fibrinogen (g/l)	2–4.5	1.13	1.07	2.26	Not done
D-Dimer (ng/ml)	<500	Not done	2,930	Not done	Not done
Ferritin (µg/ml)	140–700	57,962	734.4	16.1	109.6
Triglyceride (mmol/l)	0–15	3.4	1.52	2.03	1.5
HIV Ab/Ag		Not detected	Not done	Not done	Not done
CMV DNA (copies/ml)		Not detected	Not done	Not done	Not done
EBV DNA (copies/ml)		Not done	1,023	Not done	Not done
Anti-nuclear antibodies		Negative	Not done	Not done	Not done
Thyroid stimulating hor-mone (mIU/l)	0.4–464	0.54	0.8	0.67	0.62

* Reference values displayed are used for adult men at Royal Victoria Hospital Montreal, Canada. Reference values may vary from one population to another and from one hospital to another.

Table 1. Blood lab results at presentation, on discharge, and at 2- and 8-month follow-up.

DISCUSSION

HLH is a severe systemic inflammatory disorder that is characterised by fever, cytokine release syndrome, cytopenia and multi-organ failure[3,4]. An emerging trigger of HLH seems to be related to the usage of ICIs, including nivolumab. Only a handful cases of HLH have been reported contrasting with the frequent other irAEs that can affect up to 40% of patients receiving immunotherapy[4,5]. The development of autoimmunity on ICIs can predict cancer response, as indicated by the total disappearance of liver metastasis post-HLH in our patient. However, although not contraindicated, some reports showed association between pre-existing autoimmune diseases and severe irAEs[6-8]. The absence of the feature of haemophagocytosis in the bone marrow biopsy did not exclude the diagnosis, as haemophagocytosis can occur outside the bone marrow in the spleen and/or the liver. The cytokine storm may have contributed to the decrease of the three haematopoietic lineages. The patient's clinical features including fever, confusion with pancytopenia, elevated ferritin, hypofibrinogenemia, elevated TG and hepatitis strongly indicated HLH. The combination of relevant clinical manifestations with key laboratory markers led to a validated H-score of 263, strongly supporting the diagnosis of HLH.

Cancer type	Autoimmune disease	PD1 inhibitor	Haemopha-gocytic lym-phohistio-cytosis (HLH) occurrence in relation to PD1 inhibitor use	Treatment	Outcome
49-year-old male thymic carcinoma[17]	Psoriasis	Pembrolizumab	1 year after initiating pembrolizumab	Steroids, intravenous immunoglobulin, and anakinra	Patient deceased
50-year-old female thymic carcinoma[6]	Sjogren's syndrome	Pembrolizumab	7 days after initiating pembrolizumab	Dexamethasone and etoposide	Patient survived
70-year-old male lung squamous cell carcinoma[6]	Positive for anti-nuclear antibodies, absence of auto-immune disease	Pembrolizumab	7 days after initiating pembrolizumab	Dexamethasone, etoposide	Patient survived

Table 2. Cases of HLH induced by PD-1 inhibitors in patients with pre-existing autoimmune disease.

When treated early, HLH can be managed with steroids and addressing the underlying trigger. However, severe forms may require intravenous immunoglobulin and/or anti-cytokines interleukin-1 inhibitors[4,9], and/or chemotherapy such as etoposide, in addition to steroids.

The timing of HLH onset in this case occurring at the seventh cycle of his anti-PD-1 suggests the presence of an unidentified trigger or resulting from a cumulative effect of the immunotherapy. We have summarised HLH case reports secondary to PD-1 inhibitors in *Table 2*. We did not find any case of HLH related to anti-HER2 usage[10,11]. Of note, the use of steroid for the treatment of irAEs did not negate the anti-cancer effect of ICIs.

HLA B27 gene polymorphism is associated with a predisposition to autoimmune diseases, including ankylosing spondylitis, anterior uveitis and recurrent HLH[12,13]. Mechanistically, HLA B27 presentation of microbial peptides cross-reacting to self-antigens leads to CD8+ cytotoxic T lymphocytes activation, a function directly enhanced by the anti-PD-1 therapy[14]. Thus, HLA polymorphisms are currently being explored as a possible factors predicting ICI-induced irAEs such as diabetes and thyroid dysfunction[5]. Thus, the mechanism is probably related to disrupted self-tolerance following ICI, resulting in autoimmunity[15]. In one study with 530 participants, no association was found between HLA polymorphisms and haematologic irAEs[16].

CONCLUSION

This report presents a rare manifestation of HLH occurring post-immunotherapy in a patient with HLA B27-positive ankylosing spondylitis, underlining a possible relationship between these factors. While the mechanism associating HLA B27 and ICI-induced HLH remains poorly understood, future studies will be needed to explore the relationship between autoimmunity and severe irAEs such as HLH and tumour response, ultimately guiding clinicians in risk assessment and personalised patient care.

REFERENCES

1. Esfahani K, Elkrief A, Calabrese C, Lapointe R, Hudson M, Routy B, et al. Moving towards personalized treatments of immune-related adverse events. *Nat Rev Clin Oncol* 2020;**17**:504–515.
2. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol* 2014;**66**:2613–2620.
3. Wiseman D, Lin J, Routy J-P, Samoukovic G. Haemophagocytic lymphohistiocytosis in an adult with postacute COVID-19 syndrome. *BMJ Case Rep* 2021;**14**:e245031.
4. Soy M, Atagündüz P, Atagündüz I, Sucak GT. Hemophagocytic lymphohistiocytosis: a review inspired by the COVID-19 pandemic. *Rheumatol Int* 2021;**41**:7–18.
5. Les I, Martínez M, Pérez-Francisco I, Cabero M, Teijeira L, Arrazubi V, et al. Predictive biomarkers for checkpoint inhibitor immune-related adverse events. *Cancers (Basel)* 2023;**15**:1629.
6. Wei Y, He W, Sun W, Wu C, Ren D, Wang X, et al. Hemophagocytic lymphohistiocytosis in two patients following treatment with pembrolizumab: two case reports and a literature review. *Transl Cancer Res* 2022;**11**:2960–2966.
7. Abdel-Wahab N, Shah M, Lopez-Olivo MA, Suarez-Almazor ME. Use of immune checkpoint inhibitors in the treatment of patients with cancer and preexisting autoimmune disease: a systematic review. *Ann Intern Med* 2018;**168**:121–130.
8. Ibis B, Aliazis K, Cao C, Yenyuwadee S, Boussiotis VA. Immune-related adverse effects of checkpoint immunotherapy and implications for the treatment of patients with cancer and autoimmune diseases. *Front Immunol* 2023;**14**:1197364.
9. La Marle S, Richard-Colmant G, Fauvernier M, Ghesquières H, Hot A, Sève P, et al. Mortality and associated causes in hemophagocytic lymphohistiocytosis: a multiple-cause-of-death analysis in France. *J Clin Med* 2023;**12**:1696.
10. Buchanan WW, Kean CA, Rainsford KD, Kean WF. Spondyloarthropathies and arthritis post-infection: a historical perspective. *Inflammopharmacology* 2024;**32**:73–81.
11. Epistola R, Chao J, Lee J. Evolving landscape of targeted treatment options for HER2-positive gastric/gastroesophageal adenocarcinomas. *Clin Adv Hematol Oncol* 2023;**21**:312–320.
12. Park JH, Seo YM, Han SB, Kim KH, Rhim JW, Chung NG, et al. Recurrent macrophage activation syndrome since toddler age in an adolescent boy with HLA B27 positive juvenile ankylosing spondylitis. *Korean J Pediatr* 2016;**59**:421–424.
13. Chang H, Shin Y-W, Keam B, Kim M, Im S-A, Lee S-T. HLA-B27 association of autoimmune encephalitis induced by PD-L1 inhibitor. *Ann Clin Transl Neurol* 2020;**7**:2243–2250.
14. Trautmann L, Janbazian L, Chomont N, Said EA, Gimmig S, Bessette B, et al. Upregulation of PD-1 expression on HIV-specific CD8+ T cells leads to reversible immune dysfunction. *Nat Med* 2006;**12**:1198–1202.
15. Singh N, Hocking AM, Buckner JH. Immune-related adverse events after immune check point inhibitors: understanding the intersection with autoimmunity. *Immunol Rev* 2023;**318**:81–88.
16. Jiang N, Yu Y, Zhang M, Tang Y, Wu D, Wang S, et al. Association between germ-line HLA and immune-related adverse events. *Front Immunol* 2022;**13**:952099.
17. Laderian B, Koehn K, Holman C, Lyckholm L, Furqan M. Association of hemophagocytic lymphohistiocytosis and programmed death 1 checkpoint inhibitors. *J Thorac Oncol* 2019;**14**:e77–78.