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CASE REPORT

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Secondary hemophagocytic lymphohistiocytosis due to nivolumab/ipilimumab in a renal cell cancer patient—A case report

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Abstract

Secondary immune-related hemophagocytic lymphohistiocytosis is a rare but life-threatening complication of immune checkpoint inhibitors. HLH-2004 and HLH-1994 guidelines originally developed for primary HLH are the only available guidelines. It has proven to have a good prognosis if diagnosed promptly with discontinuation of immunotherapy and treated with corticosteroid monotherapy.

KEYWORDS

hematology/oncology, HLH, immune checkpoint inhibitors, ipilimumab, nivolumab, pembrolizumab, secondary hemophagocytic lymphohistiocytosis

1 | INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of the immune system resulting from the loss of the delicate hemostasis maintained by natural killer (NK) cells and cytotoxic lymphocytes. It can be primary or secondary, and etiology can be multifactorial such as viral infection, autoimmune disorder, or malignancies.[1] According to studies and depending on underlying etiology, mortality with HLH ranges from 26.5 to 74.8%.[2] With the recent development of immune checkpoint inhibitors (ICIs) and their frequent use in advanced cancers, immune-related adverse events (irAEs) are increasingly being recognized. One of such adverse events (AEs) is immune-related HLH (irHLH). NK cells and cytotoxic lymphocytes are responsible for producing a perforin (protein), which keeps cytokine production under check by inducing pores in macrophages. Loss of this negative feedback system due to ICIs helps with tumor destruction and results in concomitant unchecked destruction of various host cells leading to multiorgan failure. Destruction of blood cells by macrophages, for example, manifests as severe pancytopenia on peripheral smear and bone marrow biopsy. We present a case of irHLH in

a patient treated for metastatic renal cell carcinoma with combination therapy of nivolumab and ipilimumab. We also present a brief literature review of irHLH secondary to ICIs (Table 1).

2 | CASE REPORT

A 68-year-old gentleman with a past medical history of hypertension, coronary artery disease, and impaired glucose tolerance in September 2020 presented with hematuria and required coil embolization of the segmental left renal artery branch to treat a left renal angiolipoma. One month after initial presentation, he had a CT scan followed by an MRI of the abdomen significant for a malignant appearing upper pole right renal mass, a suspicious appearing lower pole left renal enhancing nodule, and multiple left renal bleeding angiolipomas. The patient also had multiple enhancing lesions in the body of the pancreas with possible splenic invasion, highly suspicious for malignancy. Subsequently, an endoscopic ultrasound-guided biopsy of the pancreatic lesion demonstrated clear cell renal carcinoma favoring metastasis. The patient was diagnosed with stage IV cT2a cNx pM1 clear cell renal cell carcinoma. He started first-line immunotherapy with ipilimumab 1 mg/kg and nivolumab 3 mg/kg every three weeks. He completed four cycles of dual immunotherapy and was transitioned to maintenance nivolumab 420 mg every four weeks.

Three months after initiation of ICI therapy, he presented to the hospital with the symptoms of decreased appetite, dizziness, generalized weakness, and declining performance status. On examination, the patient was found to have intermittent fevers with associated tachycardia. Initial workup was significant for symptomatic hyponatremia and pancytopenia. Subsequent workup demonstrated extremely high ferritin levels of 57,931 ng/ml, pancytopenia with WBC count 1.1 (reference range (RR): 3.6–11.2 $\times$ 10^9/L), absolute neutrophils 0.7 (RR: 1.6–7.0 $\times$ 10^9/L), hemoglobin 7.7g/dl (RR: 13–18g/dl), hematocrit 22.1% (RR: 39%–54%), platelet count of 46 (RR: 150–400 $\times$ 10^9/L, and hyponatremia with serum sodium of 122 mmol/L (RR: 136–144mmol/L). Differential diagnoses included sepsis, undiagnosed hemochromatosis, disease progression with infiltrative bone marrow involvement, and irHLH. He was treated accordingly with a thorough infectious workup, supportive transfusions, antibiotic therapy, restaging scans, and nephrology consultation for management of symptomatic hyponatremia.

Since the patient received dual ICIs and was still on nivolumab for maintenance, irHLH was strongly suspected. Further workup was significant for hypofibrinogenemia of 148 mg/dl (RR: 200–393 mg/dl), hypertriglyceridemia of 338 mg/dl (RR: <150 mg/dl), very low NK cell activity of 12 cells/MCL (RR: 59–513) and sCD25 > 4000. CT abdomen and pelvis were also significant for splenomegaly. Bone marrow (BM) biopsy was without evidence of hemophagocytosis and showed non-specific BM hyperplasia (Figures 1 and 2). The lack of dyspoiesis suggested peripheral consumption, destruction, or sequestration of blood components as a possible etiology of pancytopenia. There was no evidence of disease progression, infectious etiology, infiltrative renal cell carcinoma of the bone marrow, or hemochromatosis.

The patient was diagnosed with irHLH based on HLH-2004 guidelines as he satisfied 6 out of 8 criteria (fever, splenomegaly, increased ferritin, hypofibrinogenemia/hypertriglyceridemia, pancytopenia involving all three cell lines, elevated sCD25, and low NK cell activity). HScore was calculated to be 233, indicative of a high predictive value for secondary HLH. He was treated with intravenous dexamethasone 6 mg every 6 h for ten days, then 6 mg every 12 h. The patient was transitioned to a slow oral dexamethasone taper based on HLH-1994 protocol.[3] He improved rapidly with the resolution of fever within five days of starting the high-dose steroid, and he was discharged home after 17 days of hospitalization. Laboratory abnormalities of irHLH resolved in four weeks with repeat laboratories significant for WBC 11 $\times$ 10^9/L, hemoglobin 14.6 g/dl, hematocrit 43.7%, platelet count 72 $\times$ 10^9/L, and fibrinogen 148 mg/dl.

3 | DISCUSSION

Current research on advanced cancers has led to the advent of immune checkpoint blocking agents. Aggressive cancers seem to use these checkpoints to evade the host immune system, leading to unchecked tumor growth and metastasis.[4] For example, PDL1 expressed by the tumor cells binds PD-1 receptors on T cells leading to their exhaustion. Humanized monoclonal IgG4 anti-PD-1 antibodies such as pembrolizumab and nivolumab overcome the immune resistance by blocking these PD-1 receptors without causing T-cell exhaustion rendering the tumor cells prone to the host immune system.[4] Similarly, T-cell activation under normal circumstances activates an expected cascade where cytotoxic T-lymphocyte antigen-4 (CTLA-4) is upregulated, resulting in negative feedback leading to downregulation of the T-cell mediated immune system. This mechanism maintains a state of balance in the immune system of a healthy person. Ipilimumab, a humanized monoclonal IgG1 anti-CTLA-4 antibody, inhibits this checkpoint in

the immune system, enhancing the T cell–mediated immunity to help the host's immunity fighting off the cancer cells.[5] Histopathology in irHLH is significant for the generalized activation of lymphocytes with excess mature macrophages in the absence of the feedback loops. It is usually associated with undetectable NK cell activity, elevated cytokines such as sIL2r in serum and CSF. Bone marrow, spleen, liver, and lymph node examination may be positive for hemophagocytosis.[6]

The ICIs have become a mainstay to treat many advanced malignancies especially metastatic melanoma and lung cancer. Most patients can tolerate single immunotherapy with mild irAEs such as skin rash, colitis, inflammatory arthritis, and hepatitis.[7,8] However, increased use of combination immunotherapies such as nivolumab and ipilimumab is now leading to an increased incidence of severe irAEs such as myasthenia gravis, myocarditis, pneumonitis, and the rare condition of irHLH.[8,9] MD Anderson Cancer Center reported a 34% incidence of any irAE with immunotherapies, but no such study existed for irHLH due to high mortality and underdiagnosis.[10] According to Saadat et al., only 50% cases of irHLH due to ICIs are detected and appropriately treated since no standard diagnostic criteria exist, making it a disease associated with high mortality.[11] In the absence of irHLH specific diagnostic criteria, most experts agree upon using HLH-2004 diagnostic criteria that favor a positive diagnosis if 5 out of 8 criteria are met, including fever, splenomegaly, cytopenia of at least two lineages, hypertriglyceridemia/hypofibrinogenemia, low NK cell activity, no evidence of malignancy, elevated ferritin levels, elevated soluble interleukin-2 receptor levels (sIL-2r also known as soluble CD25 or sCD25), and hemophagocytosis in BM, spleen, or lymph nodes.[6] The fact that hemophagocytosis on BM is one of the eight criteria and not a requirement to make the diagnosis of HLH is noteworthy, as evident from our case (Figures 1 and 2).

Numerous mutations in the perforin gene are a well-known genetic abnormality in primary HLH.[12] It is not well studied if these mutations also contribute toward irHLH. We identified only one irHLH case report in our literature search that was tested and found heterozygous for the PRF1 gene.[13] It is difficult to ascertain whether HLH in our case is secondary to immunotherapy alone or a combination of advanced malignancy and ICIs.[11] Our search of Clinicaltrials.gov and Cochrane database did not result in any clinical trials that are in progress on irHLH; this might be due to a negligibly small number of those patients. Literature review of PubMed showed 12 case reports related to ICIs apart from our case (Table 1).

The time of irHLH onset varies greatly among various ICIs. All patients with nivolumab/ipilimumab induced irHLH, including our case ($n = 4/13$) started symptoms after 4 cycles of therapy. On the contrary, pembrolizumab-induced irHLH showed a greater variation of onset as evident in the table (1 week to 9 months of initiation of immunotherapy).

Treatment of irHLH includes the discontinuation of immunotherapy. Most cases, including ours (7/13, 54%), were treated with high-dose corticosteroid monotherapy and responded well. Three out of 13 patients (23%) were treated with a combination of corticosteroids and etoposide based on HLH 2004 criteria, and they also recovered well. Lorenz et al. reported one case of irHLH (8%) that did not respond to corticosteroids but subsequently responded to tacrolimus monotherapy.[14] Satzger et al. also reported one patient (7%) treated with a combination of corticosteroids and mycophenolate motif and did well.[15] One patient in reported cases (8%) was not diagnosed on time nor received treatment resulting in death (irHLH was confirmed on autopsy).[16] Thus far, there is no consensus on treatment for irHLH, but most patients (10/13, 77%) seem to respond well to corticosteroid monotherapy or combination therapy per HLH-2004 protocol. All irHLH patients in the literature review who received treatment (12/13, 92%) resulted in resolution of HLH (Table 1), thus indicating an excellent prognosis with ICIs-related cases. Liu et al. reported positive results with nivolumab monotherapy for relapsed/refractory EBV-related HLH in adults in an unrelated case series (71.4% with complete remission after 16 months median follow-up). This approach has not been tested for irHLH but might need careful evaluation and investigation with refractory cases.[17,18] Since immunotherapies have proven to be beneficial for refractory or relapsed cases of cancer, once these patients develop irHLH, subsequent treatment options are extinct, limited, or suboptimal for many advanced cancers.[19] One potential option would be to rechallenge patients with the previous irHLH with immunotherapies; however, studies have not been conducted to evaluate the incidence of recurrent severe immune-related AEs such as irHLH.

4 | CONCLUSION

IrHLH is a rare but life-threatening complication of ICIs if left untreated. The increasing utilization of ICIs for advanced cancers can lead to increasing incidence of IrHLH. Therefore, it is highly important to diagnose it at an early stage. It has a good prognosis if diagnosed in a timely

TABLE 1 Treatment and Outcomes of Immune-Related Hemophagocytic Lymphohistiocytosis Case Reports

Author (Year)	Age (Sex)	Diagnosis	Monoclonal antibody	Onset of HLH
Chin et al[19]	69 (F)	Metastatic melanoma	Ipilimumab /nivolumab	Finished 4 cycles of ipilimumab/nivolumab and was on nivolumab maintenance therapy fortnightly
Hantel et al[7]	35 (F)	Metastatic melanoma	Ipilimumab /nivolumab	Failed 4 cycles of adjuvant ipilimumab with worsening metastasis, then started on combination ipilimumab /nivolumab. HLH developed 3 weeks post cycle 1.
Sadaat et al[11]	58 (M)	Metastatic melanoma	Pembrolizumab	31 days after finishing 6 cycles/doses.
Satzger et al[15]	26 (F)	Metastatic melanoma	Ipilimumab /nivolumab	Almost 4 weeks after finishing 4 cycles of both ipilimumab and nivolumab (3 weekly intervals).
Thummalapalli et al[16]	74 (M)	Glioblastoma	Nivolumab /BMS−986205	Cycle 2 of treatment
Okawa et al[20]	78 (M)	SCC of lung	Pembrolizumab	10 days after first dose of pembrolizumab
Akagi et al[21]	74 (M)	Advanced ADC of lung and RA	Pembrolizumab	27 days after first dose of pembrolizumab
Al-Samkari et al[13]	58 (F)	Metastatic ductal-CA of breast	Pembrolizumab /eribulin	Developed HLH during cycle 5
Sasaki et al[22]	60 (F)	Metastatic melanoma	Pembrolizumab followed by Dabrafenib/trametinib	Developed HLH 6 weeks after finishing 7 cycles of pembrolizumab and 2 weeks after dabrafenib/trametinib
Lorenz et al[14]	68 (M)	Metastatic prostrate cancer	Pembrolizumab /enzalutamide /gonadotropin releasing hormone anaolog	No mention of a timeline of HLH development
Shah et al[23]	76 (M)	Metastatic bladder cancer	Pembrolizumab	Developed HLH after 9 months of immunotherapy
Takahashi et al[24]	78 (M)	Advanced ADC of lung	Pembrolizumab	7 days after first dose of pembrolizumab
Our case (2021)	68 (M)	Metastatic renal cell CA	Ipilimumab /nivolumab	Finished 4 cycles of ipilimumab/nivolumab and received one cycle of nivolumab maintenance, with HLH development in one week.

Abbreviations: Hb, Hemoglobin, PLT, Platelets, NK cell, Natural killer cell, WBC, White cell count, +ve, Positive, −ve, Negative, BM, Bone marrow, ADC, Adenocarcinoma, SCC, Squamous cell carcinoma, EBV, Epstein-Barr virus, Q6H, 6 hourly, Q12H, 12 hourly, PO, Oral, MMF, Mycophenolate motif.

Symptoms/Signs	Biopsy	Treatment	Outcome
Fever, hepatosplenomegaly, bilateral edema. **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↓fibrinogen, ↑triglyceride, ↑sCD25, ↓NK cell activity	BM +ve for hemophagocytosis	Methylprednisolone 1500 mg daily for 3 days followed by taper over 2 months.	6 Weeks
Fever, splenomegaly, bilateral edema. **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↑triglyceride, ↑sCD25,	BM +ve for hemophagocytosis	Methylprednisolone 1.5 mg/kg for 4 days, then 1mg/kg oral prednisone for 1 month. Then tapered gradually to chronic dose for a history of panhypopituitarism.	6 Months
Splenomegaly **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↑triglyceride, ↓NK cell activity	Not done	Oral prednisone 1mg/kg/day for 5 weeks, then tapered over the next 7 weeks.	7 Weeks
Fever **Laboratories:** ↓Hb, ↓PLT, ↓WBC, ↑ferritin, ↓fibrinogen,	Liver biopsy +ve for macrophage activation	Prednisone 2 mg/kg/day for 1 week, then prednisone 1.5mg/kg/day with MMF 360 Q12H, then prednisone 1 mg/kg/day with MMF 720 Q12H.	1 week
Fever, splenomegaly, Altered mental state. **Laboratories:** ↑Ferritin, ↓Hb, ↓PLT, ↓WBC	On autopsy, elevated sCD25, spleen, and BM +ve for hemophagocytosis.	Not treated	Pt was not diagnosed in time leading to his demise.
Fever, splenomegaly **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↑sCD25, ↓NK cell activity	BM +ve for hemophagocytosis	Steroid pulse therapy with taper, dosage, and duration not mentioned.	Recovered but no mention of timeframe.
Fever, hepatosplenomegaly **Laboratories:** ↓Hb, ↓WBC, ↑ferritin	BM +ve for hemophagocytosis	Dexamethasone 10mg/m^2 and etoposide 150 mg/m^2. Subsequently tapered per HLH−2004 protocol.	5 Weeks
Fever, rash **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↓fibrinogen, ↑triglyceride, ↑sCD25	Heterozygous +ve for PRF1A91V	High-dose methylprednisolone (initial dose 1g with taper) with 11 doses of etoposide 150mg/m^2 for 8 weeks.	4 Weeks
Fever, hepatosplenomegaly, rash **Laboratories:** ↓Hb, ↓PLT, ↓WBC, ↑ferritin	BM +ve for hemophagocytosis	Prednisolone 0.5mg/kg/day	5 Weeks
Fever, hepatosplenomegaly **Laboratories:** ↓Hb, ↓PLT, ↓WBC, ↑ferritin, ↓fibrinogen, ↑triglyceride, ↑sCD25,	BM +ve for hemophagocytosis	Incomplete response to high-dose steroids, plasmapheresis, and cyclosporin A. Pt subsequently responded to tacrolimus monotherapy.	Recovered but timeframe not mentioned
Fever, splenomegaly, rash **Laboratories:** ↓Hb, ↓PLT, ↓WBC, ↑ferritin, ↓fibrinogen, ↑sCD25, ↓NK cell activity	BM +ve for hemophagocytosis, EBV PCR also +ve.	High-dose dexamethasone and etoposide per HLH−2004 protocol.	Outcome not mentioned
Fever **Laboratories:** ↓Hb, ↓PLT, ↑ferritin, ↓fibrinogen, ↑sCD25	BM +ve for hemophagocytosis	Methylprednisolone 1000mg/day for 3 days, then oral prednisolone 1 mg/kg/day (60mg/day) for 4 weeks, then oral prednisolone 50mg/day.	4 Weeks
Fever, splenomegaly **Laboratories:** ↓Hb, ↓PLT, ↓WBC, ↑ferritin, ↓fibrinogen, ↑triglyceride, ↑sCD25, ↓NK cell activity	BM -ve for hemophagocytosis	IV dexamethasone 6mg Q6H for 10 days, then 6mg Q12H. Now on slow PO dexamethasone taper.	4 weeks

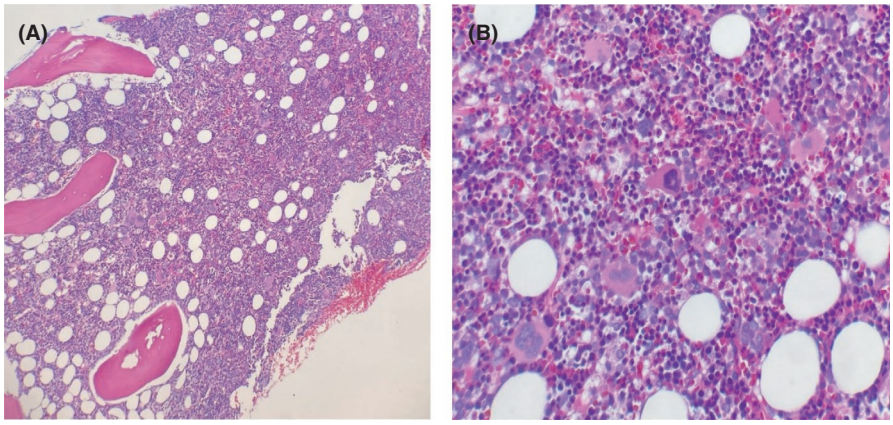

FIGURE 1 Bone marrow biopsy (hematoxylin and eosin Stain) showing hypercellular bone marrow. Magnification (A) 100 times (B) 400 times

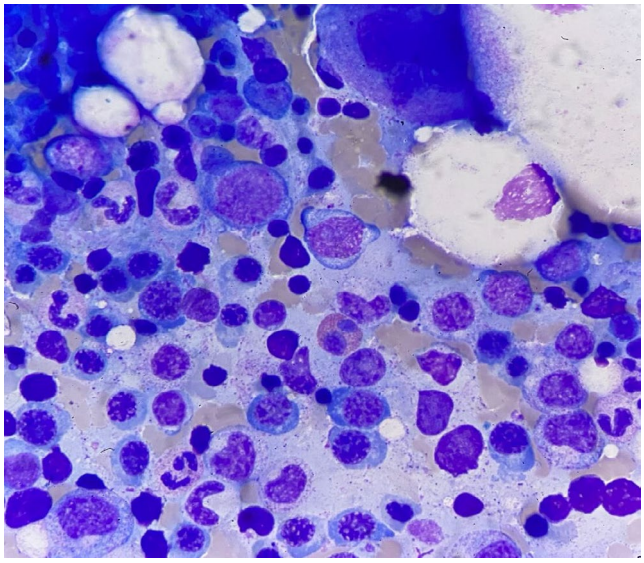

FIGURE 2 Bone marrow aspirate smear showing trilineage hematopoiesis and no histiocytes containing nucleated hematopoietic precursors (hemophagocytosis). Magnification 1000 times, Wright Giemsa stain

fashion and treated with discontinuation of ICIs and corticosteroid monotherapy compared to primary HLH. Currently, the irHLH is diagnosed if five of eight criteria are met based on HLH-2004 guidelines.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Adeel Masood, Walid El Ayass, Tanya Clifford, and Ahsan Wahab made a substantial contribution to conception, design, and interpretation of data. He has been involved in drafting the manuscript, given final approval of the version to be published, and agreed to be accountable for all aspects of the work. Eric J. Weaver made a substantial contribution to the conception, and design of the pathology slides. He has been involved in the manuscript drafting, given final approval of the version to be published, and agreed to be accountable for all aspects of the work. Hamid Ehsan made a substantial contribution to the design, interpretation of data. He has been involved in the manuscript drafting, given final approval of the version to be published, and agreed to be accountable for all aspects of the work.

CONSENT

Informed and written consent was obtained from the patient.

DATA AVAILABILITY STATEMENT

Data and patient charts are available at request.

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