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Case Report

A Case Report of Immune Checkpoint-Related Hemophagocytic Lymphohistiocytosis and Review of the Literature

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Abstract
Introduction: Hemophagocytic lymphohistiocytosis (HLH) secondary to immune checkpoint inhibitors (irHLH) is rare, and consequently optimal management strategies remain to be defined. There are sparse reports of the successful treatment of irHLH with steroids and tocilizumab. This case adds to the body of literature supporting this management strategy. ***Case Description:*** We present a case of a patient with thoracic malignancy who received dual checkpoint inhibitors and developed weakness, fever, confusion, and cytopenias. Further testing revealed an extremely elevated ferritin level. Cytokine levels as well as HLH-2004 criteria and HScore results were consistent with irHLH. Clinical parameters and symptoms promptly improved after the administration of corticosteroids and tocilizumab. ***Conclusion:*** This case highlights an important treatment strategy for an immune checkpoint inhibitor toxicity associated with a high mortality rate.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disorder characterized by hyperinflammation and aberrant activation of cytotoxic T cells and macrophages in response to various triggers. Primary HLH is more commonly seen in the pediatric population and is due to inherited mutations affecting immune regulation and lymphocyte cytotoxicity, whereas secondary HLH is

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more common in adults and is seen in response to malignancy, infection, autoimmune disorders (as in the case of macrophage activation syndrome), or immunosuppression. Malignancy associated HLH (M-HLH) may be triggered by the malignancy itself or due to the therapy used to treat the malignancy (ICI, cellular therapy) [1]. The clinical phenotype often includes the triad of fever, cytopenias, and splenomegaly [2]. The diagnosis of HLH can be challenging due to overlapping features with sepsis and multiorgan dysfunction. No single clinical or laboratory finding has sufficient sensitivity or specificity to make a diagnosis of HLH. Proposed diagnostic criteria such as HLH-2004 are largely derived from pediatric literature and have not been validated in the adult population [3]. The HLH-probability calculator (HScore) was retrospectively developed in an adult population and is available as an online calculator to assist with diagnosis [4]. The optimized HLH inflammatory index (OHI), comprising CD25 >3,900 U/mL and ferritin >1,000 ng/mL was validated in adult patient with hematologic malignancy and was found to have better test characteristics for HLH diagnosis and prognosis in this population [5]. HLH is associated with a poor prognosis, and frequently progresses to fatal cytokine storm and multiorgan failure in the absence of prompt treatment. For this reason, clinicians may proceed with empiric treatment for patients with evidence of a rapidly progressive course before diagnostic confirmation has been achieved. Treatment of HLH varies based on the etiology but in general consists of immunosuppression, chemotherapy, or biologics. Commonly, primary HLH is treated with the HLH-94 protocol consisting of dexamethasone, cyclosporine, intrathecal therapy and etoposide, with or without allogeneic stem cell transplant [2]. In secondary HLH, treatment is not standardized and must be modified based on the underlying condition. More recent evidence has linked immune checkpoint inhibitors (ICI), including anti-programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte associate protein 4 (CTLA-4) antibodies with the development of secondary, ICI-related HLH (irHLH). Tocilizumab is a humanized monoclonal antibody against interleukin-6 (IL-6) receptor that has shown efficacy in the treatment of disorders of hyperinflammation with excessive cytokine production such as COVID-19 and chimeric antigen receptor cell associated cytokine release syndrome (CRS). Emerging data suggests that ICI related HLH can be successfully treated with corticosteroids and anti-IL-6 receptor therapies such as tocilizumab [6]; however, the number of cases reported in the literature is small.

Case Presentation

The CARE Checklist has been completed by the authors for this case report, attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000539955). A 76-year-old man was treated with palliative intent for a poorly differentiated carcinoma involving the left pleura, mediastinal lymph nodes and bone. Biopsy results indicated atypical epithelioid and spindle cells with extensive necrosis. On immunohistochemistry the atypical cells were positive for pankeratin (AE1/AE3), low molecular weight keratins (CAM 5.2), CK7, with patchy weak staining for CK20, weak staining for GATA3, and focal staining for CK5/6. The cells were negative for TTF-1, p63, calretinin, WT1, BerEp4, EMA, MSA, desmin, CD34, Bcl-2, and S100. D2-40 was positive in scattered cells. Claudin-4 and monoclonal CEA were negative. The overall findings were not entirely definitive with respect to the tumor type; however, sarcomatoid carcinoma of pulmonary origin was somewhat favored with the differential diagnosis including biphasic or sarcomatoid malignant mesothelioma. PD-1L staining was greater than 50%, and next generation sequencing (NGS) testing was negative for targetable mutations. Given this the decision was made to proceed with nivolumab (4.5 mg/kg q 3 weekly) and ipilimumab (1 mg/kg q 6 weekly) with two cycles of carboplatin area under the curve (AUC) 6 and paclitaxel 175 mg/m^2 followed by ongoing nivolumab and ipilimumab maintenance. Follow-up imaging demonstrated a partial

response of the patient's malignancy to therapy. The patients' other comorbidities included hypertension, hypothyroidism, dyslipidemia, benign prostatic hypertrophy, and depression.

Six months after starting treatment, and 6 days after the most recent nivolumab dose the patient was admitted to hospital with 7 days of increasing lethargy, diminished appetite, mild abdominal discomfort, and an episode of confusion in which he became disoriented and lost his way driving from his home at night. On presentation, he was found to be febrile with a maximum temperature of 39°C with notable fluctuation in orientation and attentiveness in hospital. On examination, there was no evidence of skin rash, abdominal tenderness, distention, guarding or rigidity, but there was palpable splenomegaly 3 cm below the costal margin. Initial work up revealed hemoglobin 76 g/L (normal range 130–170), platelets 52 × 10^9/L (normal range 150–440), white blood cells 2.7 × 10^9/L (normal range 4–11), reticulocytes 8 (normal range 10–100), haptoglobin <0.1 g/L (normal range 0.3–2), INR 1.4 (normal range 0.8–1.2), PTT 77 s (normal range 27–42), fibrinogen 2.5 g/L (normal range 1.9–4.7) (see Table 1 for full clinical details). Peripheral blood smear review by hematopathology revealed pancytopenia but no evidence of schistocytes. Creatinine was 70 μmol/L (normal range 64–111), AST was 126 U/L (normal range 5–34), albumin was 27 g/L (normal range 32–46), sodium was 125 mmol/L (normal range 136–145), bilirubin was normal; LDH was 1,897 U/L (normal range 125–220). Ferritin was >200,000 μg/L (normal range 21.8–275), triglycerides were 1.42 mmol/L (normal <1.70). Blood and urine cultures were drawn and revealed no growth of bacteria after at least 5 days of incubation. As thrombotic thrombocytopenic purpura (TTP) was initially on the differential diagnosis, ADAMSTS13 activity was sent and was normal.

Magnetic resonance imaging (MRI) of the brain with gadolinium enhancement revealed scattered foci of increased signal intensity on T2 and T2 FLAIR weighted sequences which were favored to represent sequelae of chronic post ischemic white matter demyelination. There were no findings suspicious for encephalitis. Computed tomography (CT) scan of the abdomen with iv contrast revealed circumferential bowel wall thickening of the ascending colon with evidence of pneumatosis and mild surrounding induration, the spleen was enlarged at 14.3 cm in length, there was no hepatomegaly.

HLH was diagnosed on the basis of achieving 5 of 8 criteria of the HLH-2004 protocol, including: fever, splenomegaly, cytopenias involving multiple cell lines, elevated serum ferritin, elevated soluble IL-2 levels. The calculated HScore was 188 indicating a 70–80% likelihood of HLH. The patient was treated empirically with high dose steroids, with dexamethasone at a dose of 20 mg orally daily for 5 days, and a single dose of tocilizumab at 8 mg/kg prior to the availability of cytokine results given the high suspicion for irHLH. Although some guidelines suggest treatment interruption and corticosteroids alone may be sufficient in the treatment of irHLH, we elected to treat with tocilizumab given the patient had organ dysfunction that could be characterized as common terminology criteria for adverse events (CTCAE) version 5 Grade 3 or higher (anemia, hemolysis requiring transfusion, cognitive dysfunction).Blood for cytokine testing was sent to an outside institution due to the inability to perform this test at our local institution. Bone marrow biopsy was completed 1 day after empiric therapy was started and revealed a hypercellular marrow, myeloid hyperplasia with left shift, scattered CD68 histiocytes were seen; however, hemophagocytic histiocytes were not seen. There were no features of myeloproliferative neoplasm, myelodysplatic syndrome, plasma cell neoplasm, lymphoproliferative disorder, or metastatic neoplasm. Cytokine levels were sent prior to initiating therapy and returned elevated. CXCL9 was 83,072 pg/mL (normal <657), IL-6 was 78.1 pg/mL (normal <3.7), sIL-2R/CD25 was 17,389 pg/mL (normal 606–2,299). The optimal cutoff for elevated sIL-2R as reported in the HLH-2004 criteria was 2,400 U/mL using a functional assay. It is important to note the reference center in the present case used an ELISA assay reporting in units of pg/mL. Although there is no established conversion factor between units, Dik, W. found high

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Table 1. Patient characteristics at presentation

	Result (normal range)
Age	76
Malignancy	Sarcomatoid carcinoma of pulmonary origin. PD-L1 >50%, no driver mutations detected
Cancer therapy	Nivolumab 4.5 mg/kg q 3 weekly and ipilimumab 1 mg/kg q 6 weekly with two cycles of carboplatin AUC 6 + paclitaxel 175 mg/m^2 followed by nivolumab + ipilimumab maintenance
Prior cycles	6
Symptoms	Lethargy, diminished appetite, mild abdominal discomfort, confusion, and fever
Hemoglobin	76 g/L (130–170)
WBC	2.7 × 10^9/L (4–11)
Platelets	52 × 10^9/L (150–440)
Reticulocytes	8 (10–100)
Haptoglobin	<0.1 g/L (0.3–2)
INR	1.4 (0.8–1.2)
PTT	77 s (27–42)
Fibrinogen	2.5 g/L (1.9–4.7)
Blood smear	Pancytopenia with no evidence of schistocytes
ADAMSTS13	Normal
Creatinine	70 μmol/L (64–111)
AST	126 U/L (5–34)
Albumin	27 g/L (32–46)
Sodium	125 mmol/L (136–145)
Bilirubin	8.5 μmol/L (3.4–20.5)
LDH	1,897 U/L (125–220)
Ferritin	>200,000 μg/L (21.8–275)
CRP	122.6 mg/L (<5)
Triglycerides	1.42 mmol/L (<1.70)
Lipase	37 U/L (8–78)
Microbiology	Blood cultures negative, urine culture, stool culture, *C. difficile* testing negative
	CMV IgG reactive, CMV IgM nonreactive
	EBV IgG reactive, EBV IgM nonreactive
Autoimmune panel	Rheumatoid factor negative, anti-CCP negative, ANA positive 1:80, C3, C4 levels normal
Cytokine levels	CXCL9: 83,072 pg/mL (<657)
	IL-6: 78.1 pg/mL (<3.7)
	sIL-2R/CD25: 17,389 pg/mL (606–2,299)
Bone marrow biopsy results	Hypercellular marrow, myeloid hyperplasia with left shift, scattered CD68 histiocytes were seen; however, hemophagocytic histiocytes were not seen. No features of myeloproliferative neoplasm, myelodysplatic syndrome, plasma cell neoplasm, lymphoproliferative disorder, or metastatic neoplasm.

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correlation between assay types (r^2 = 0.99) [6] with a value of 17,389 pg/mL corresponding to approximately 2,500 U/mL. Transfusion support with packed red blood cells and pooled platelets were given in hospital.

Following initiation of tocilizumab and steroids there was rapid improvement in the patient's clinical status and laboratory parameters. He remained afebrile with improvement of his mental status back to baseline (see Fig. 1 for the trend of select laboratory values). The patient was transitioned to oral prednisone with a tapering course over 3 weeks. He was maintained on proton pump inhibitor and pneumocystis jiroveci pneumonia (PJP) prophylaxis while on steroids. There were no identified adverse events associated with steroid or tocilizumab therapy. He was discharged from hospital on day 16 after treatment. Cytokine levels were rechecked on day 24 and were as follows: sIL-2R 2,526 pg/mL, IL-6 186 pg/mL, and CXCL-9 1,386 pg/mL. CT scan was repeated after discharge and showed evidence of disease progression within the chest. The patient was transitioned to systemic chemotherapy with carboplatin and pemetrexed and rechallenge with immunotherapy was not attempted due to the concern of HLH reactivation.

Discussion

HLH is a disorder of immune hyperactivation in response to a variety of stimuli that can progress to multiorgan dysfunction and death. Diagnostic criteria such as HLH-2004 and the HScore can aid in diagnosis. Immune checkpoint inhibitors (ICIs) such as those targeting PD-L1 and CTLA-4 increase activation of cytotoxic T cells and are increasingly used in the management of multiple tumor types. As the use of ICI increases, there have been a growing number of reports of development of HLH as an immune-related adverse event (irAEs). Although historically primary HLH has been managed using a combination of dexamethasone, etoposide and, cyclosporine, alternative management strategies have been developed for cases secondary to ICIs [2], with particular interest in agents inhibiting IL-6 signaling. As the number of immune modulating therapies being used in the clinic grows, the complex nature of HLH pathogenesis and optimal management, depending on the trigger, is emerging. This fact is highlighted by studies showing that nivolumab, a PD-L1 inhibitor implicated in triggering HLH, has also been used as a potential management strategy of EBV associated HLH [7]. Furthermore, JAK inhibition with ruxolitinib [8], and IFN gamma inhibition with emapalumab [9] are emerging as additional potential targets in the immumodulatory pathway to treat HLH. We present a case of HLH associated with ICI use, successfully treated with corticosteroids and tocilizumab.

One of the first case series reporting the successful treatment of ICI associated HLH with tocilizumab was published by Ozdemir et al. [10]. The authors showed that 3 patients with melanoma who were diagnosed with irHLH exhibited Th1 cytokine profiles including elevated IL-6. Functional T cell studies showed high activation of CD8+ T cells and Th1 polarization of CD4+ T cells. Cytokine levels as well as clinical parameters improved rapidly post initiation of corticosteroids and tocilizumab with a median duration of corticosteroid tapering of only 21 days.

A systematic review by Rajapakse [11] identified 22 cases of HLH associated with ICI. The most common clinical findings included fever, anemia, thrombocytopenia, and elevated ferritin. All patients received PD-1/PD-L1 inhibitors with 9 also receiving CTLA-4 inhibitors with a time to HLH ranging between days to 1 year. All patients received treatment with corticosteroids for HLH, while 5 patients also received etoposide, 5 received anti-IL-6 blockade, 1 received IVIG, and 3 received alternative immunosuppressives, reflecting a lack of defined guidelines of management. Three patients died from HLH. Three patients were rechallenged with ICI with no recurrence of HLH. Liu et al. [12] conducted a systematic review of cases of HLH and cytokine release syndrome associated with ICI and identified 49 articles

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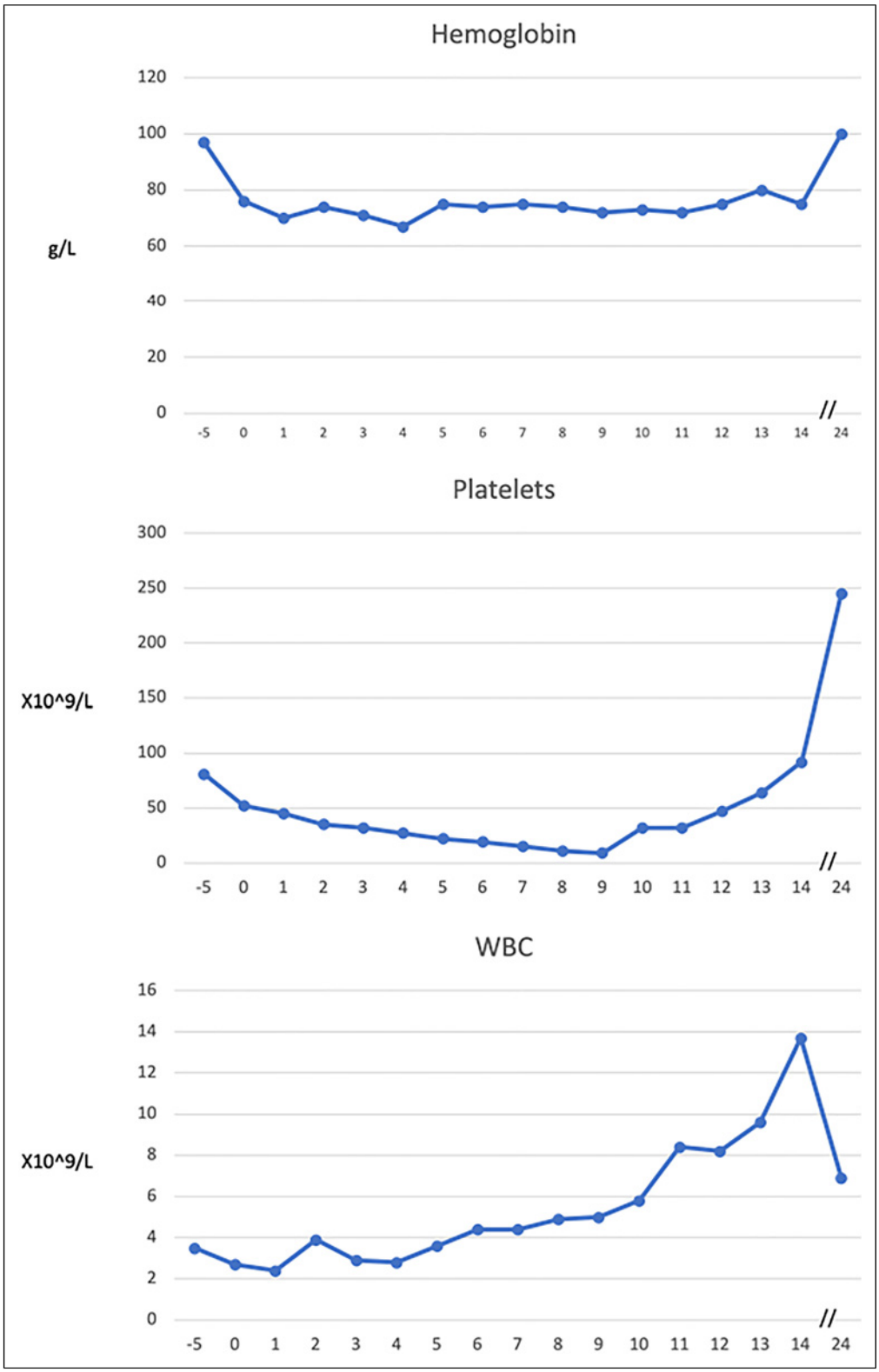

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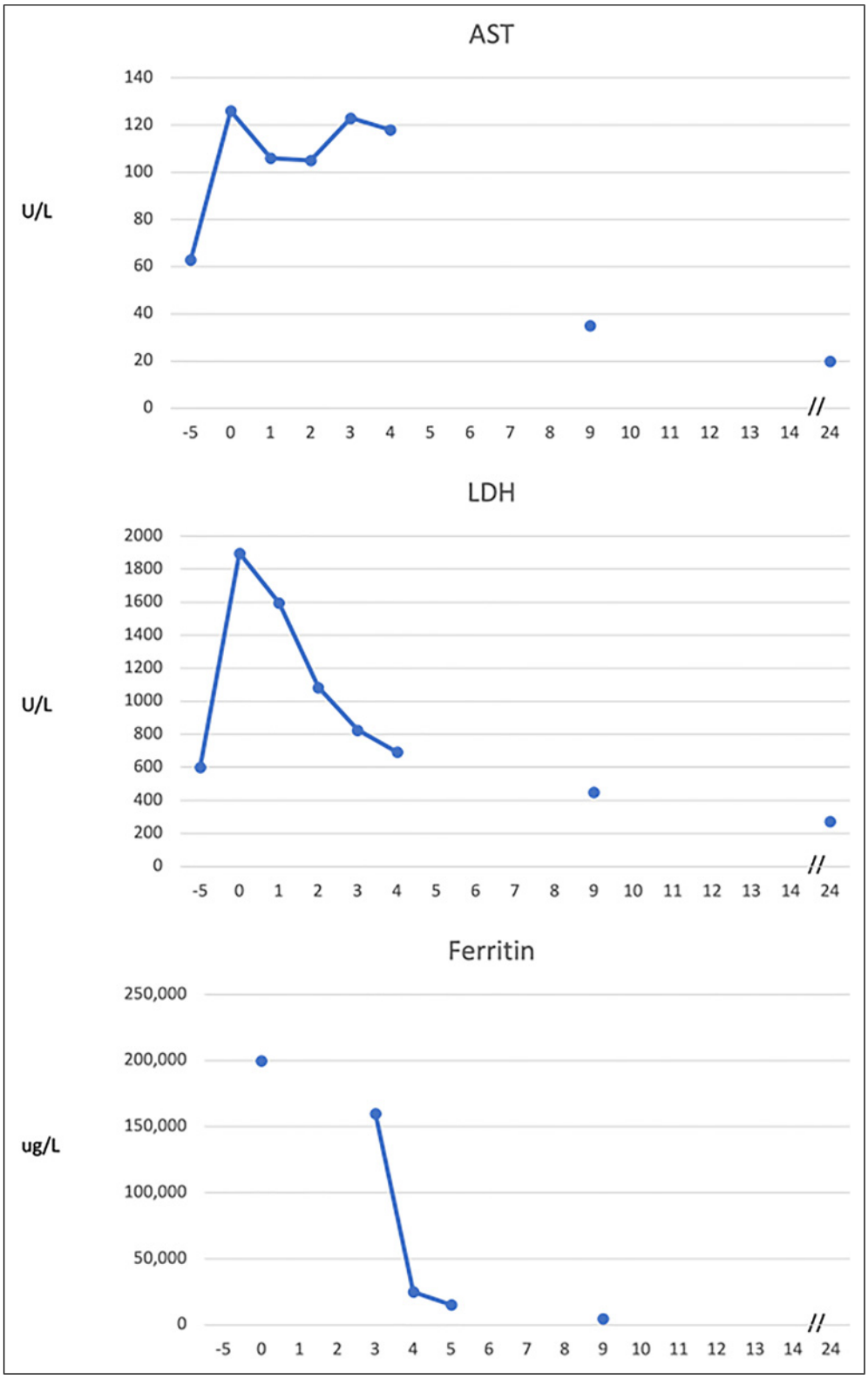

Fig. 1. Trend of laboratory values throughout treatment course. X-axis measured in days. Treatment with tocilizumab and corticosteroids started on day 0.

including 189 patients from case reports, case series or queries of pharmacovigilance databases. They reported that the definitions of CRS and HLH varied significantly and retrospective diagnostic assessment was not always possible. Most cases had received single agent PD-1/PD-L1 therapy with 25% receiving combination PD-1/PD-L1 and CTLA-4 therapy. The mortality rate from HLH was 11%. All patients were treated with corticosteroids, with 25% receiving tocilizumab. Interestingly, none of the patients treated with tocilizumab had a fatal outcome, although 1 patient had a recurrent episode of HLH which was fatal. The heterogeneity of management approaches for irHLH in the literature reflects its rarity in clinical practice. The latest management guidelines on immune-related adverse events of ICI published by the European society for medical oncology (ESMO) [13] state that anti-IL-6R therapy may be used for irHLH, largely based on the case series by Ozdemir et al. The American society of clinical oncology (ASCO) guidelines on the management of irAEs does not discuss irHLH.

Conclusions

Our case report adds to the limited body of literature showing irHLH is a rare side effect of ICI therapy. Strengths of our case report include documentation of cytokine and laboratory parameters at the time of diagnosis and after therapeutic intervention. Weaknesses of our case report include the fact that we were unable to perform immunophenotyping on blood or bone marrow samples at the time of diagnosis or after therapy. We show that patients can be successfully treated with the combination of corticosteroids and tocilizumab with improvement in cytokine and clinical parameters, and that this therapy is well tolerated. These data adds to the confidence of this therapeutic strategy for patients who develop irHLH. As the number of patients treated with ICIs increases, it will be important to recognize this rare but important irAE and to build evidence of effective therapies.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. As per Halton Healthcare institutional guidelines and SOP, case reports do not require institutional REB approval.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

M.H., A.L., S.F., and S.D. participated in clinical management and decision making, M.H. collected patient data, performed the literature review, and prepared the manuscript. M.H., A.L., S.F., and S.D. edited the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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