



Case Report

Diverse Triggers of Macrophage Activation Syndrome

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) represents a critical, potentially fatal condition marked by disproportionate activity within both the innate and adaptive immune systems. Predominantly observed in oncological contexts, HLH has seen a rising incidence over recent years. Here, we present two cases that underscore the different origins of secondary HLH in cancer patients: one triggered by immune checkpoint inhibitors and another by Hodgkin's lymphoma. These instances illustrate the complexity of the diagnosis and management of HLH, especially if resulting as a consequence of immunotherapy. Moreover, each case sheds light on the intricate interaction between therapeutic agents and the immune system's regulatory capacity, offering insights into the spectrum of HLH etiologies and emphasizing the need for prompt monitoring and management.

List of Abbreviations: ABVD: Doxorubicin, Bleomycin, Vinblastine and Dacarbazine; CMV: Cytomegalovirus; CRP: C-reactive protein; CRS - Cytokine released syndrome; DD: Differential Diagnosis; DIC: Disseminated Intravascular Coagulation; EBV: Epstein-Barr Virus; HIV: Human immunodeficiency virus; HLH: Hemophagocytic lymphohistiocytosis syndrome; HScore: Hemophagocytic syndrome Score; HSV: Herpes simplex virus; ICIs: Immune checkpoint inhibitors; IFN γ : Interferon γ ; IL: Interleukine; IPS: International Pronostic Score; MAS: Macrophage Activation Syndrome; OS: Overall survival; PY - Pack year; spp: species; TNF α : Tumor Necrosis Factor α .

Keywords: Macrophage Activation Syndrome; Hemophagocytic Lymphohistiocytosis; Immune Checkpoint Inhibitors; Hodgkin Syndrome; Hematology; Oncology.

Introduction

Hemophagocytic lymphohistiocytosis (HLH) represents an uncontrolled inflammatory syndrome clinically characterized by fever, reduced blood counts, and hyperferritinemia. A triad prompting the initiation of complementary investigations and fast intervention due to its rapid evolution towards multiorgan failure if left untreated (Cox et al. Lancet Rheumatol., 2024), immune dysregulation, typified by hyperferritinemia and the overactivation of T lymphocytes and macrophages, culminating in a cytokine storm. The North American Consortium for Histiocytosis (NACHO) reframes HLH, distinguishing 'HLH Disease' from

'HLH Disease mimics', the former attributable to innate or acquired immunodeficiency and the latter unrelated to immunosuppression. Rheumatological HLH, or macrophage activation syndrome (MAS-HLH), bears the standard nomenclature in English-speaking regions, and we adopt herewith 'secondary HLH' for the following patient cases. Secondary HLH is a life-threatening complication of various etiology. In order of frequency, hematological malignancies constitute nearly a third of HLH causes, followed by infectious and rheumatological diseases, with primary HLH representing <5% of cases [1]. Hepatomegaly and splenomegaly accompany the above-mentioned clinical- biological triad in nearly two-third of cases as consequence of increased T cell and macrophage proliferation, frequently associated with disseminated intravascular coagulation (DIC) [2-5].

Central to HLH pathophysiology are immune cells CD8+ and NK T lymphocytes, and macrophages which orchestrate wound healing, host defense, and immune regulation in the physiological setting. In healthy conditions, cytotoxic T-cells and macrophages mediate target cell destruction through perforin/granzyme release for the first and phagocytosis for the second cell subtype. In HLH, however, a failure in this cytotoxic function, through genetic mutations (primary HLH) or immune dysregulation (secondary HLH), leads to rapid cytokine release and ineffective cell lysis. Primary HLH typically manifests in infancy, necessitating etoposide+/- ciclosporin A (following HLH-94 or -2004 protocols) followed by allogeneic stem cell transplantation, while secondary HLH can arise at any age due to cancer, infection, autoimmune condition, but also without an identifiable trigger (idiopathic HLH) [6]. Laboratory findings encompass worsening pancytopenia, accompanied by anti-inflammatory syndrome indicated by hyperferritinemia and hypertriglyceridemia because of macrophage hyperactivation and an acute phase reaction. The diagnosis, lacking a gold standard, follows the HLH-2004 criteria or the HS Score (i.e. HScore), which estimates the likelihood based on biological markers. The HScore allows earlier diagnostic recognition compared to HLH-2004 criteria and should be repeated over time in parallel to clinical and biological evolution of suspected cases. Ferritin levels above 10'000 ug/L were shown to have a high sensitivity and specificity ($\geq 90\%$) for HLH diagnosis in a retrospective study [7]. Though hemophagocytosis on bone marrow examination is routine, it's neither definitive nor exclusive to HLH given its appearance in non-HLH intensive care patients [8-11]. HLH treatment relies on causative treatment such as chemotherapy in the case of associated malignancy, often accompanied by T-cell directed immunosuppressive therapy including etoposide, glucocorticoids, ciclosporin A, anti-thymocyte serum, JAK-STAT inhibitors, and immunomodulatory therapy including intravenous immunoglobulins in case of severe/refractory HLH, rheumatological-HLH, and HLH caused by innate (primary HLH) or acquired immunodeficiency. Cytokine blockade targeting TNF α , IL-1, IL-6R, IL-18 can be discussed as it has proven activity in cases of primary HLH, and as part of causative treatment in the case of rheumatological-HLH. HLH related to EBV reactivation should be treated with anti-CD20 monoclonal antibodies [12]. Prognosis varies, being most dire for HLH secondary to hematological malignancies, followed by autoimmune, viral, and idiopathic forms [13,14] (Table 1).

Here we present two cases that elucidate the divergent etiologies of secondary HLH in the oncological setting: one driven by immunotherapy-induced immune dysregulation and the other caused by Hodgkin's lymphoma. These cases exemplify the complexity of HLH diagnosis and management, underscoring the heterogeneity of its pathogenesis where therapeutic interventions

such as immunotherapy can inadvertently trigger HLH, and malignancies like Hodgkin's lymphoma can lead to an aberrant immune response manifesting as HLH. Each case serves to display the intricate interplay between therapeutic modalities and the immune system's capacity for dysregulation, contributing valuable insights into the spectrum of HLH etiologies.

Case Presentation

Case 1 - 71-year-old Caucasian patient with a relapse of malignant cutaneous melanoma.

The first case is a 71-year-old Caucasian patient with a relapse of malignant cutaneous melanoma, initially Breslow 2.7 mm, pT3a pN0 (0/1) cM0, stage IIA according to AJCC 8th edition, excised 5 years before the relapse and known to be an active smoker at 45 PY. At relapse, the patient was diagnosed with gastric metastasis of the BRAF- and MEK-negative mutations melanoma that had also metastasized to the liver and lymph nodes. Checkpoint inhibitors with anti-CTLA4 (ipilimumab) and anti-PD1 (nivolumab) was started, along with five sessions of radiotherapy to the stomach. One week after the 2nd cycle of immunotherapy, the patient consulted the emergency department because of a drop in general condition and a fever since the previous day, with no other complaints. On clinical examination, the patient had fever at 38.8°C, tachypnea and oxygen saturation at 90%. Laboratory findings showed a mild inflammatory syndrome with no leukocytosis, anemia at 105g/L, thrombocytes within the limit at 150 G/L with no sign of hemolysis. He rapidly developed acute liver and kidney failure, which necessitated his transfer to intensive care. D-dimer were at 13,000ng/ml (normal range < 500ng/ml) and PTT was prolonged. Initially, a urinary tract infection and autoimmune hepatitis were suspected. Treatment with antibiotics and methylprednisolone 250mg IV was started. The patient's general condition rapidly deteriorated, with persistent fever, hypoxemia and respiratory distress, however hemodynamically stable. Laboratory findings showed a massive increase in liver enzymes, a slight increase in bilirubin, together with increased ferritin > 25,000 μ g/L, hypertriglyceridemia, a massively increased (334pg/ml) IL6 and CRP, progressive pancytopenia with thrombocytopenia and leukopenia, with stable hemoglobin, low fibrinogen and D-dimers > 35'00 ng/ml. In this context, a differential diagnosis of macrophage activation syndrome was suspected as well as a cytokine release syndrome (CRS). At that moment, the HS score was 246 points, implying a 99% chance of HLH. At the same time, the patient also fulfilled the biological criteria for DIC. In this context, the treatment was modified: the patient received tocilizumab (8mg/kg), followed by a maintenance of methylprednisolone 250mg IV per day for 3 days, followed by a tapering regimen starting at 1mg/kg/day. The patient's general condition rapidly improved, with normalization of biological values and clinical stabilization.

Case 2 - 42-year-old patient diagnosed with classic Hodgkin’s lymphoma.

The second case is a 42-year-old patient diagnosed with Hodgkin’s lymphoma of mixed cellularity subtype, stage IV, IPS Score 5 (Hasenclever) with bone, splenic involvement, and bilateral cervical and axillary adenopathy. During the staging period, the patient consulted the emergency department with severe asthenia and inappetence, with daily diurnal and nocturnal febrile states. Laboratory findings showed an inflammatory syndrome with increased CRP, new pancytopenia, new cytolysis, and cholestasis, increased ferritin levels >11,000 ug/l and acute renal failure. Procalcitonin was increased (4.51µg/l.). Abdominal ultrasound showed splenomegaly and a liver of normal size and appearance. An HLH was suspected with considering as well CRS or septic shock as differential diagnoses. At this point, the SH score was 252 points, implying a 99% chance of HLH. Antibiotic treatment was started, as well as the pre-phase chemotherapy with prednisone 100 mg p.o. for five days, and blood transfusion. 48 hours after arrival, the patient had undergone the final staging examinations, and treatment for Hodgkin’s lymphoma was started. Due to hemodynamic instability, the patient was transferred to intensive care unit, where he received one cycle of the ABVD chemotherapy protocol (Doxorubicin, Bleomycin, Vinblastine and Dacarbazine) at an adapted dose to renal and hepatic function. The patient’s biological values and general condition rapidly improved.

Trigger/Etiology	Abdelhay & al, 2023 N : 16136	Ramos-Casals & al, 2014 N : 2197	Trigger/Etiology	Abdelhay & al, 2023 N : 16136	Ramos-Casals & al, 2014 N : 2197
Infection	24,3%	3913	50,4%	1108	
Viruses	21,6%	3491	34,7%	762	
EpsteinBarr virus	5,5%	893	15,0%	330	
HIV	4,4%	710	7,9%	173	
Herpes viruses	4,4%	702	3,4%	74	
Cytomegalovirus	4,9%	794	3,1%	69	
Viral hepatitis	5,1%	818	0,9%	20	
Influenza	1,1%	184	0,6%	14	
Human parvovirus B	0,7%	109	0,6%	14	
Other viruses or not specified	N/A	N/A	3,1%	68	
Bacteria	1,7%	279	9,4%	206	
Mycobacterium tuberculosis	0,7%	120	3,6%	78	
Rickettsia spp	1,0%	159	0,8%	17	
Staphylococcus spp	N/A	N/A	0,7%	15	
Escherichia coli	N/A	N/A	0,5%	11	
Other bacteria or not specified	N/A	N/A	3,9%	85	
Parasites	0,4%	70	2,4%	53	
Leishmania spp	N/A	N/A	0,8%	17	
Plasmodium spp	N/A	N/A	0,6%	14	
Toxoplasma spp	0,2%	25	0,5%	10	
Other parasites	0,1%	15	0,5%	12	
Babesia spp	0,2%	30	N/A	N/A	
Fungi	2,2%	349	1,7%	37	
Histoplasma spp	1,8%	294	0,8%	18	
Other fungal infections	0,3%	54	0,9%	19	
Infection not specified	N/A	N/A	2,3%	50	
Other / no trigger identified	35,8%	5782	7,1%	157	
Other circumstances	N/A	N/A	3,5%	76	
Drugs	N/A	N/A	0,9%	20	
Surgery or biopsies	N/A	N/A	0,5%	11	
Vaccination or acute injuries	N/A	N/A	0,5%	10	
Diabetes or chronic liver disease	N/A	N/A	0,6%	14	
Pregnancy	N/A	N/A	0,5%	11	
Haemodialysis	N/A	N/A	0,5%	10	
Other or not specified	N/A	N/A	0,6%	13	
Idiopathic or unknown	N/A	N/A	3,7%	81	
Malignancy	30,7%	4953	47,7%	1047	
Hematologic	28,6%	4619	44,7%	981	
Lymphoma	19,7%	3171	N/A	N/A	
NonHodgkin Lymphomas NHL	16,9%	2727	N/A	N/A	
B-cell NHL	5,8%	935	15,2%	333	
T-cell NHL	7,1%	1153	16,8%	369	
Unspecified NHL	4,4%	708	1,6%	35	
Hodgkin lymphoma HL	2,9%	464	2,8%	61	
Leukemia	9,1%	1463	3,0%	67	
Lymphoid leukemias	2,8%	445	N/A	N/A	
Myeloid leukemias	4,7%	752	N/A	N/A	
Myeloproliferative diseases	1,4%	231	N/A	N/A	
Unspecified leukemia	0,5%	85	N/A	N/A	
Plasma cell dyscrasias	1,7%	275	N/A	N/A	
Castleman disease	N/A	N/A	1,0%	22	
Other haematological neoplasms	N/A	N/A	4,3%	94	
Solid	2,7%	434	1,5%	32	
Not specified neoplasm	N/A	N/A	1,5%	34	
Autoimmune conditions	20,8%	3362	12,6%	276	
Connective tissue diseases CTD	18,6%	2998	11,1%	244	
Systemic lupus erythematosus	6,7%	1088	6,1%	133	
Adultonset Still's disease	N/A	N/A	2,5%	54	
Rheumatoid arthritis	7,7%	1235	0,8%	18	
Vasculitis	2,3%	374	0,5%	11	
Other or not specified	2,5%	404	1,3%	28	
Organ specific	N/A	N/A	1,5%	32	
Infl ammatory bowel disease	2,5%	404	0,5%	11	
Other diseases	N/A	N/A	1,0%	21	
Congenital immunodeficiency synd.	2,5%	399	N/A	N/A	
Transplantation	4,0%	639	4,3%	95	
Kidney transplant	1,2%	191	2,4%	53	
Bone marrow transplant	1,3%	204	1,3%	29	
Other organ transplant	1,6%	254	0,6%	13	

Table 1: Pathologies associated with Hemophagocytic lymphohistiocytosis syndrome. Adapted from:Adult hemophagocytic syndrome, Ramos et al. 2014 / Epidemiology, characteristics, and outcomes of adult hemophagocytic lymphohistiocytosis in the USA, 2006–19: a national, retrospective cohort study, Abdelhay et al. 2023.

Diagnosotic and therapeutic response	Case 1	Case 2
Hscore		
Known immunosuppression	NO	Hodgkin Lymphoma
Temperature [°C]	39.5	39.6
Hepatomegaly	No	Yes
Splenomegaly	No	Yes
Low hemoglobin level [120-160 g/L]	89	68
Low leucocytes level [4.0-10.0 Gpt/L]	1,1	1,1
Low platelets count [150-370 Gpt/L]	71	46
Higher ferritin level [50-350 g/L]	49	11
Higher triglyceride level [<2 mmol/L mmol/L]	4.12	1.7
Low fibrinogen level [2.0-4.5 g/L]	0,7	5
High ASAT level [<40 UI/L]	1,151	877
Hemophagocytes features in the bone marrow aspirate	N/A	N/A
Total HScore - points	246	252
Probability of HS [%]	99	99
Therapy		
First line	Prednisone	Prednisone Chemotherapy with ABVD
Second line	Tocilizumab	Not applicable
Time to resolution [days]	7	5
Outcome		
Best response	Partial response	Complete remission
OS after 6 months	YES	YES

Table 2: HScore and therapeutic response of case 1 and case 2. Green depicts positive diagnostic features, red negative features. Normal range in brackets. Abbreviations: ABVD - chemotherapy protocol using Doxorubicin (A), Bleomycin (B), Vinblastine (V), Dacarbazine (D), OS - overall survival.

Discussion and Conclusion

These cases highlight the diversity of cancer associated secondary HLH etiologies as a rare complication in the context of advanced malignancies and immunotherapeutic interventions. The first case underscores the immunological sequelae of checkpoint inhibitor therapy, manifesting as hemophagocytic lymphohistiocytosis (HLH) with a superimposed DIC, responding favourably to high-dose steroid therapy and IL-6R blockade with tocilizumab. In fact, recent studies suggest an incidence of 0.03%-0.4% of HLH secondary to immune checkpoint inhibitors with a mortality rate of up to 50% [15]. The second case illustrates the challenge of diagnosing HLH in the setting of advanced Hodgkin's lymphoma, treated by the initiation of chemotherapy, where the differential diagnosis includes CRS and sepsis. Both cases exemplify the critical need for vigilance and prompt management in patients presenting with hyperinflammation and multi-organ involvement.

These cases emphasize the importance of considering HLH in the differential diagnosis of patients with malignancy who develop systemic inflammatory symptoms without inflammatory focus, particularly when receiving immunomodulatory therapies. Fever accompanied

by worsening cytopenia, should prompt laboratory assessment of ferritin and triglyceride levels, together with an emphasis on detecting the presence of hepato-splenomegaly during physical examination or radiological assessment due to its occurrence in nearly two-third of cases. Further laboratory assessments should encompass liver and kidney function tests together with complete coagulation tests including fibrinogen measurement. Cytokine profiling including plasma measurements of TNF α , IL-1, IL-6, IL-10, IL-12, and IFN γ , together with circulating levels of soluble IL-2 receptors (sIL2R or sCD25), and CD163 are not mandatory and not validated for management decisions, however, along with bone marrow examination, they might be considered for research purposes. The rapid improvement with targeted treatments demonstrates the efficacy of timely intervention, albeit highlighting the necessity for continued research into the optimal diagnosis and management strategies for HLH in the oncologic setting. Moreover, these cases underline the importance of rare but fatal side effects of novel treatments for cancer, where the benefits must be balanced against the potential for severe immune-related adverse events.

Declaration

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