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Case Report

Management of Secondary Hemophagocytosis Lymphohistiocytosis with Severe Liver Dysfunction

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Abstract

Introduction: Hemophagocytosis Lymphohistiocytosis (HLH) is a syndrome of inappropriate hyperimmune response.

Presentation of Case: We present a case of secondary HLH associated with systemic lupus erythematous (SLE) and liver dysfunction.

Conclusion: This case report focuses on the diagnostic dilemmas with HLH and an individualized treatment approach to the patient.

Keywords: Hemophagocytosis Lymphohistiocytosis; liver dysfunction

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Introduction

Hemophagocytosis Lymphohistiocytosis (HLH) is a syndrome of inappropriate hyperimmune response[1].It has been described as Primary or Familial (due to gene mutation) or Secondary HLH (due to a specific trigger e.g. malignancy – 38%, infection – 32%, autoimmune disease – 12%)[2]. HLH associated with rheumatologic diseases is termed as macrophage activation syndrome (MAS)[3]. The excessive tissue inflammation and organ dysfunction in HLH is due to dysregulation of cytotoxic T-cells, Natural killer (NK) cells and macrophages with associated increased secretion of cytokines[3].Due to rarity of this syndrome, no clear guidelines for its management have been established, especially in adult population. Most of our current knowledge has been based on studies done in children. Here we present a case of secondary HLH associated with systemic lupus erythematous (SLE) in an adult – the diagnostic dilemma it posed and an individualized treatment approach to the patient.

Case Description

A 24-year-old Hispanic female with history of recently diagnosed systemic lupus erythematous (SLE) presented to our hospital with fever, abdominal pain with nausea and vomiting worsening for 2 months. She was evaluated at an outside clinic 4 weeks ago for similar presentation and was diagnosed with SLE. Patient refused medical treatment and opted for herbal therapy at that time. There was no significant family history. On presentation she was febrile to 102F but hemodynamically stable. Physical examination was remarkable for erythematous indurated plaqueson face and bilateral hands, oral ulcers and RUQ abdominal tenderness. No organomeglyor lymphadenopathy was palpated. Initial diagnostic work-up was remarkable for deranged liver enzymes (ALP 166U/L, GGT 157U/L, AST 199U/L and ALT 189U/L), LDH 535U/L, ANA+ >1:160 (speckled), DS- DNA 57IU/ml (Normal 0-4IU/ml), low complements and elevated ESR. The hemoglobin (Hb) was 10.8g/dL,white cell count 2.8k/µL and platelet count 69k/µL. She was found to have ferritin of 7123ng/ml. Extensive infectious work up (bacterial, viral and fungal) and toxicology screen was negative. Computed tomography (CT) scans revealed hepatomegaly, bilateral axillary, mediastinal and right hilar lymphadenopathy (LAD). Spleen size was normal. A presumptive diagnosis of secondary HLH or MAS associated with SLE was made. She had skin, liver, axillary LAD and bone marrow biopsy with no malignancy on pathology. Bone marrow biopsy revealednormocellular marrow with no atypical cells. She received empiric broad-spectrum antimicrobial therapy initially but was discontinued due to no improvement in clinical condition. She also received pulse steroid therapy but her symptoms and laboratory parameters deteriorated significantly (Table 1). Magnetic resonance imaging (MRI) was unremarkable for obstructive etiology of worsening liver functions. Natural Killer (NK) cell activity came back low and she met the HLH-2004 diagnostic criteria.She was started on HLH-94 treatment protocol(Etoposide and dexamethasone). Given her clinical condition and severely deranged liver function she was started on very low dose of Etoposide (30mg/m2). The dose was escalated as both clinical and laboratory parameters improved (Table 2). After 2 cycles of chemotherapy, she developed altered mental status and was intubated for airway protection. She was worked up for CNS involvement of HLH. The cerebrospinal fluid analysis, MRI brain and electroencephalogramwere normal. She received weekly intrathecal Methotrexate and hydrocortisone for presumed HLH-CNS involvement. She improved

significantly and was discharged to complete chemotherapy as outpatient. After completion of 8 cycles of chemotherapy her symptoms were resolved and there was significant downtrend in laboratory parameters (Table 1 and Fig 1). She continued to have close outpatient follow up to monitor for HLH relapse.She was started on azathioprine, Plaquenil and prednisone for SLE treatment.

Table 1Trend of Laboratory Parameters

Laboratory parameters	At presentation	Peak/nadir values (before chemotherapy)	After chemotherapy completion
Albumin (g/dL)	3.4	2	4.2
Bilirubin (Total/direct) (mg/dL)	0.4/0.3	10.6/6.6	0.2/0.1
ALP/GGT/AST/ALT (U/L)	166/157/199/189	1308/1589/1716/1308	122/156/32/27
LDH (U/L)	535	2124	183
Ferritin (ng/ml)	7123	37, 632	400
PT/PTT (seconds)	13.1/53	12.5/34.1	11.4/24.5
Fibrinogen (mg/dL)	575	422	499
Triglyceride (mg/dL)	133	408	123
Serum creatinine (mg/dL)	0.4	0.4	0.4
Creatinine Clearance (ml/min)	185	185	185

Table 2 Modified HLH-94 Regimen

Cycle	Chemotherapy
C1	1. Etoposide 30mg/m2+ Dexamethasone 10mg/m2
	2. Etoposide 30mg/m2+ Dexamethasone 10mg/m2
C2	1. Etoposide 45 mg/m2+ Dexamethasone 10mg/m2
	2. Etoposide 75 mg/m2+ Dexamethasone 10mg/m2
C3	1. Etoposide 112.5 mg/m2+ Dexamethasone 5mg/m2
C4	1. Etoposide 150 mg/m2+ Dexamethasone 5mg/m2
C5	1. Etoposide 150 mg/m2+ Dexamethasone 2.5mg/m2
C6	1. Etoposide 150 mg/m2+ Dexamethasone 2.5mg/m2
C7	1. Etoposide 150 mg/m2+ Dexamethasone 1.25mg/m2
C8	1. Etoposide 150 mg/m2+ Dexamethasone tapered to zero

Discussion

The diagnosis of HLH is established by either molecular diagnosis consistent with HLH or fulfillment

of 5 out of 8 following criterion – Fever, splenomegaly, cytopenia• 2-3 lineages in peripheral blood (Hb<9g/dL, Platelets <100k/µL, neutrophils < 100/µL), hypertriglyceridemia (>265mg/dL) and/or hypofibrinogenemia (<1.5g/L), hemophagocytosis in bone marrow, spleen or lymph nodes, low or absent NK cell activity, ferritin>500 µg/L or soluble CD25 (sIL2r)>2400U/mL [4].Of note, this diagnostic criterion has not been validated in adult population that has predominantly secondary HLH. A diagnostic score to estimate risk of secondary HLH, the HScore, is freely available at saintantoine.aphp.fr/score (90% in our patient)[5]. More so, some authors have suggested MAS specific diagnostic criterion[6, 7].The distinction of primary versus secondary HLH is not needed for management of acute phase but may be required to plan long-term treatment strategy[1].Due to lack of standardized diagnostic approach, we recommend clinician to be aware of the causes of secondary HLH and have high clinical suspicion if above suggestive features are present because untreated HLH has high fatality rate. Other associated findings are hepatomegaly, hyperbilirubinemia, transaminitis, elevated LDH, CNS involvement (may have pleocytosis and/or elevated protein on CSF analysis) or skin manifestations[8].Our patient met the diagnostic criteria for HLH, although no hemophagocytosis was seen on multiple biopsies, which is neither sensitive nor specific for HLH due to sampling error and its manifestations later in disease course[9, 10].

The mainstay of HLH therapy is based on Etoposide and dexamethasone from HLH-94 treatment protocol. The regimen includes etoposide 150mg/m2 (twice weekly for 2 weeks then weekly for 6weeks) and tapered dose of dexamethasone (weeks 1 and 2 – 10mg/m2, weeks 3 and 4 – 5mg/m2, weeks 5 and 6 -2.5mg/m2, week 7 – 1.25mg/m2 and week 8 – taper dose to zero)[11]. The final results of HLH-2004 study, that included cyclosporine in the initial treatment, are still awaited. Hematopoietic Stem Cell Therapy (HSCT) may be considered in primary HLH or patients who have disease relapse or refractory to HLH-specific therapy. Although better long-term cure has been achieved with HSCT in children age <16, it should be considered on case-by-case basis in adult population due to lack of good supportive evidence[1, 12]. In CNS involvement, weekly intrathecal hydrocortisone and methotrexate is standard of care. Every effort should be made to identify the triggering factor in secondary HLH because in a stable patient controlling the trigger itself may halt the excessive immune response negating the need for more toxic HLH specific therapy[1, 10]. In MAS, treatment of the rheumatologic disorder with pulse steroids +/- cyclosporine is the mainstay therapy but some patient may require addition of etoposide[3, 10]. In unstable patient, HLH-specific therapy should not be withheld while attempting to identify or control the trigger due to high mortality associated with HLH. Our patient's both clinical and laboratory parameters severely worsened even after she received a course pulse steroid. This led to the decision of treating her with HLH-specific therapy.

The main component of the therapy, Etoposide, is metabolized in the liver and renally excreted. A dose reduction of 25-75% is recommended based on the creatinine clearance but the dose adjustment in hepatic dysfunction is less clear[8].While some authors do not recommend dose reduction in isolated hyperbilirubinemia but in severe hepatic dysfunction, as in this patient, a dose escalation of etoposide may be considered as the liver function improves. An important point to be mentioned here is that the recommended dose of etoposide, 150mg/m2, is based on the study done in children that may be unnecessary and more toxic in adults. A maximum dose of 100mg/m2 etoposide has been suggested to minimize myelosuppression and predisposition to infection[1].Our patient received a starting dose of 30mg/m2 and with improvement in liver function, she was able to tolerate

full dose of 150mg/m2. Alemtuzumab may be a reasonable alternative to Etoposide in patients with severe hepatic dysfunction[13].

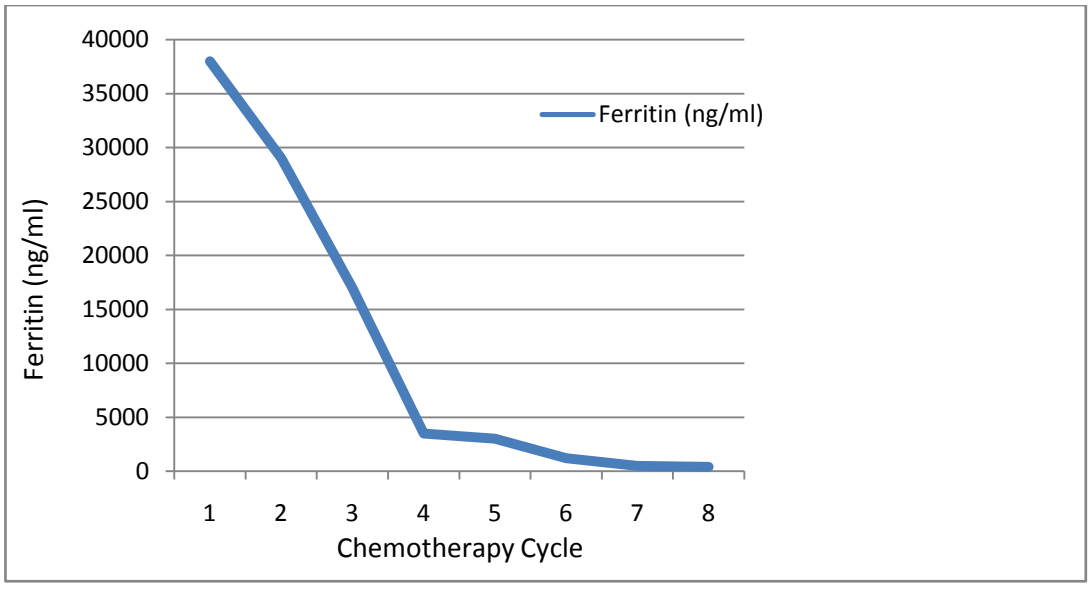
The response to therapy may be monitored by the trend of ferritin levels. Although sIL-2r(soluble IL-2 receptor) and sCD163 (a receptor for hemoglobin-haptoglobin complexes) levels are better markers of disease activity, these tests are expensive and not readily available[14].Our patient had a very good response to Etoposide dose escalation therapy with significant downtrend in ferritin, bilirubin and liver enzymes.

The treatment recommendations based on HLH-94 study may not be fully applicable to adult population. In the face of paucity of data, we recommend an individualized treatment approach to HLH in adult patients.

Learning points:

- Secondary HLH is commonly associated with malignancy, infection or autoimmune disease.
- Treating the triggering factor in secondary HLH, especially MAS may negate the need for more toxic HLH-specific therapy.
- A minority of patients with MAS may require etoposide in addition to steroids.
- Most of the HLH recommendations are based on studies done in children and a more individualized treatment approach should be opted in adult patients.

Fig. 1Trend of Ferritin Levels



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