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Case report

Desperate times, desperate measures: successful use of chemotherapy in treatment of haemophagocytic lymphohistiocytosis (HLH) due to disseminated histoplasmosis

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SUMMARY

We describe a case of haemophagocytic lymphohistiocytosis (HLH) secondary to disseminated histoplasmosis, which was treated with chemotherapy in addition to standard antifungal therapy. While HLH in the setting of infections is very well described, its treatment in this setting is controversial, with some physicians treating only the underlying infection, whereas others using immune suppression in addition to antimicrobials. To the best of our knowledge, this is the first report documenting the successful treatment of an adult patient with HLH due to disseminated histoplasmosis using etoposide chemotherapy after initial antifungal therapy failed to show improvement.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome resulting from a hyper stimulated but ineffective immune response. It is characterised by impaired function of natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) that results in an unchecked inflammatory response. Without treatment, HLH has an estimated overall mortality of 58%–75%.[1] The disorder is divided into primary (genetic) and secondary (reactive) haemophagocytic syndrome. The primary genetic disorder (familial/genetic HLH) is associated with defects in cytotoxic functioning of NK cells and CTLs and is common in children.[2] Much of the understanding of HLH in adults is based on research done in paediatric population.[3] The secondary or reactive haemophagocytic syndrome is common in adults and is associated with infections, malignancy or an autoimmune disorder (macrophage activating syndrome).[2] Since there is no single definitive test, the diagnosis of HLH is made on the basis of criteria taking into account clinical, laboratory and histopathological findings. Histopathologically, typical findings include activated macrophages with engulfed leucocytes, erythrocytes, platelets and their precursors cells. These activated macrophages are known as haemophagocytes and they may be seen in any organ, particularly in the bone marrow, lymph nodes, liver and spleen.[2] In HLH-94, the first prospective international treatment study for HLH, diagnosis was based on five criteria (fever, splenomegaly, bicytopenia, hypertriglyceridaemia and/or hypofibrinogenaemia, and haemophagocytosis). In HLH-2004, three additional criteria were introduced: low/absent NK cell activity, hyperferritinaemia and high-soluble interleukin (IL) 2 receptor levels. Altogether five of these eight criteria must be fulfilled, unless family history or molecular diagnosis is consistent with HLH.[4] Since therapy can be lifesaving and some of the clinical criteria occur late in the disease, it is not necessary to fulfil all criteria before initiating therapy.[2] The treatment of HLH involves the use of corticosteroids, chemotherapy or other drugs to block the hyperinflammatory response and specific therapy for the underlying cause. The treatment protocol as per HLH-2004 includes the upfront use of dexamethasone, etoposide and cyclosporine. Methotrexate and steroids may be given intrathecally in situations where central nervous system involvement is suspected. Haematopoietic stem cell transplantation is also a treatment option for certain groups of patients. These include patients whose disease is familial or due to a molecular risk factor and in those who have severe, persistent or reactivated disease.[4]

CASE PRESENTATION

A 44-year-old woman with medical history of ankylosing spondylitis, hypertension, nephrolithiasis, fibromyalgia and obesity presented with 5 days of fever, nausea and upper abdominal pain. She was receiving methotrexate 10 mg weekly for ankylosing spondylitis and was started on infliximab (400 mg intravenous infusion) about a month prior to her presentation. She had previously been on prednisone and hydroxychloroquine. She denied using tobacco products, alcohol or drugs and had used cannabis occasionally. On examination, she was haemodynamically stable with a temperature of 102° F, jaundiced and had a diffusely tender abdomen. Her initial laboratory tests are listed in table 1. During evaluation of elevated liver function tests, abdominal ultrasound and CT revealed gall bladder wall oedema and gallstone without dilation of the common bile duct. Hepatobiliary iminodiacetic acid (HIDA) scan was non-diagnostic and magnetic resonance cholangiopancreatography (MRCP) showed a contracted gall bladder along with non-obstructed biliary system. Viral

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Table 1 Laboratory results at the time of presentation

Laboratory parameter	Value	Normal range
Haemoglobin	97 g/L	120–155 g/L
White blood cell count	7.6×10^9/L	$3.5–10.5\times10^9$/L
Platelets	179×10^9/L	$150–450\times10^9$/L
Serum creatinine	0.6 mg/dL	0.52–1.04 mg/dL
Sodium	134 mmol/L	137–145 mmol/L
Bicarbonate	21 mmol/L	22–30 mmol/L
Total bilirubin (direct bilirubin)	6.9 mg/dL (6.2 mg/dL)	0.2–1.3 mg/dL (0–0.4 mg/dL)
Aspartate aminotransferase	445 U/L	14–36 U/L
Alanine aminotransferase	141 U/L	9–52 U/L
Alkaline phosphatase	544 U/L	38–126 U/L
Prolactin	85.2 ng/mL	3–18.6 ng/mL
Prothrombin time	15.2 s	12.1–14.5 s
Partial thromboplastin time	30 s	22–36 s
International normalised ratio	1.23	<1.1

hepatitis A, B and C and HIV were ruled out. Blood and urine cultures were ordered and intravenous antibiotics were started for suspected biliary source of infection. Because there was no convincing evidence of biliary obstruction, interventions to drain the biliary system were withheld. Over the next 72–96 hours, fever worsened (to around 103°F–104°F) and she had an episode of seizure, persistent encephalopathy, acute kidney injury (requiring sustained low efficiency dialysis), coagulopathy and worsening liver function. Electroencephalogram (EEG) showed triphasic waves and background slowing consistent with metabolic encephalopathy. A chest X-ray (figure 1) done for tachypnoea showed possible multifocal pneumonia and soon enough, she needed intubation for airway protection and vasopressors for hypotension. Also, given the persistent fevers and encephalopathy, differential diagnosis and management were broadened for the possibility of meningitis and viral encephalitis. CT of the head showed cerebral oedema and lumbar puncture showed intracranial pressure of 41 cm H_2O (5–18 cm H_2O), white blood cell count of 12/mL (0–5/mL) and protein of 51 mg/dL (15–55 mg/dL). Cerebrospinal fluid (CSF) PCR and cultures were negative for bacterial, fungal and viral infections. Given the incessant high fevers, continued clinical deterioration and negative microbial cultures, possibility of HLH was raised and appropriate workup was ordered. Initial workup for HLH revealed a ferritin level of 20 308 ng/mL (11–307 ng/mL), triglyceride level of 1409 mg/dL (40–200 mg/dL), fibrinogen level of 105 mg/dL (200–450 mg/dL) and a repeat CT scan showed mild splenomegaly. Patient fulfilled five out of eight criteria for HLH, namely, fever, cytopenia, splenomegaly, elevated ferritin and elevated triglyceride or low fibrinogen. She was started on dexamethasone 20 mg daily for concern of HLH. A liver biopsy done for worsening liver function showed granulomatous hepatitis and numerous intracellular organisms within macrophages and hepatocytes, which were morphologically compatible with *Histoplasma capsulatum*. Grocott methenamine silver (GMS) stain highlighted fungal yeast forms and given that these findings were consistent with disseminated histoplasmosis, she was started on amphotericin. *Histoplasma* antigen level in urine was ≥19.0 ng/mL, which was above the limit of quantification for the assay. Despite being on amphotericin and dexamethasone for 4 days, she did not show clinical improvement. She was started on etoposide in addition to the dexamethasone per HLH-94 protocol. A bone marrow biopsy done before initiating chemotherapy showed fungal yeast forms on GMS stain and erythrophagocytosis. Etoposide was dose reduced to 25% of original (37.5 mg/m^2) due to acute kidney injury and it was continued for a total of 2 doses only given the rapid clinical improvement.

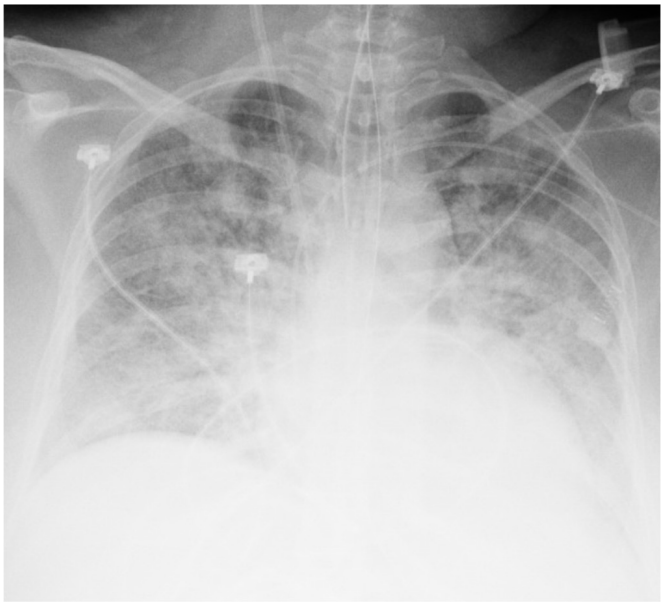

Figure 1 Chest X-ray (anteroposterior) done during the initial workup showing bilateral multifocal pneumonia.

OUTCOME AND FOLLOW-UP

Over the ensuing days, the patient improved dramatically while being carefully monitored and supported in the intensive care unit. She was eventually discharged in 2 weeks from the first dose of etoposide with the plan for dexamethasone taper over 4 weeks and long-term antifungal therapy. Soluble IL-2 receptor levels, which were sent earlier, eventually came back elevated to 24 900 pg/mL (≤1033 pg/mL) consistent with the diagnosis of HLH.

DISCUSSION

Patients with HLH present with clinical and laboratory evidence of extreme inflammation.[5] HLH is categorised as primary (familial) or secondary (acquired) and occasionally, when an inciting event is not identified, it is considered idiopathic. Also, many patients are thought to have underlying genetic susceptibility, which predisposes them to develop HLH.[3] In a large study from France done on 162 adults with HLH, the most common associated conditions were malignancy (60%), infection (25%) and autoimmune disorders (3%). The most common malignancy in this cohort was B-cell lymphoma (22%) and the most prevalent infection was *Mycobacterium* (8%). Notably, nearly half of these patients were immunosuppressed at presentation due to either HIV infection or immunosuppressive therapy.[6] In a retrospective study done on 62 adults with HLH, the most common malignancy observed was T-cell lymphoma (59%) and the most frequent infection was Epstein-Barr virus (EBV) (26%).[7] In our patient, the inciting event was immunosuppression from the use of infliximab, which led to disseminated histoplasma infection resulting in an extreme inflammatory state consistent with HLH. Opportunistic infections (OIs) are well known to be associated with the use of biologic disease-modifying antirheumatic drugs, especially tumour necrosis factor (TNF) inhibitors. Different agents within this group vary in their strength of association with OIs. For example, infliximab and adalimumab have a higher risk of OIs compared with etanercept.[8]

TNF is necessary for forming granulomas and preventing reactivation of granulomatous infections. Of note, histoplasmosis is the most common fungal OI with an estimated incidence of 18.78 per 100 000 persons (0.00018%), second only to tuberculosis with an incidence of 53.81 per 100 000 persons (0.00053%) treated with infliximab.[9] Clinical features of disseminated histoplasmosis could overlap with that of HLH in many aspects, including prolonged fever, hepatosplenomegaly, pancytopenia and coagulopathy. Given the similarity in manifestations, it may be challenging to differentiate these two conditions without specialised testing.[10] In our case, the liver biopsy which led to the diagnosis of disseminated histoplasma was prompted by the persistently abnormal liver function tests. There are several cases in the literature describing association of HLH with underlying histoplasmosis; however, majority are in the setting of HIV infection.[11] Management of HLH in the setting of infection is controversial. Antimicrobial therapy alone might be sufficient if a treatable inciting infection is identified. However, for those who are critically ill or clinically worsening, concurrent immunosuppressive therapy could also be used.[12] The seriousness of the condition is highlighted in a review of 18 HIV patients presenting with HLH in the setting of disseminated histoplasmosis, where 44.4% patients died. Not getting antifungal treatment and having *Histoplasma* in blood were the two main risk factors for death. None of the survivors among these were treated with chemotherapy or bone marrow transplant.[11] Use of anakinra, an IL-1 receptor antagonist, and dexamethasone to treat secondary HLH in a patient with HIV/AIDS and disseminated histoplasmosis that was refractory to concurrent antifungals, highly active antiretroviral therapy (HAART) and intravenous immunoglobulin (IVIG) has been described.[13]

Patient's perspective

This all started with fevers. I just thought that I had a sinus infection. I went to the doctor and received antibiotics 2 days prior to being hospitalised. I am unclear as to most of the testing and diagnosing that took place. I do not remember anything until I woke up on the vent at Henry Ford. I appreciate everything done for me during my hospital stay. My recovery has been hard, but I can now walk and do more things for myself. Thank you for everything.

Learning points

- Haemophagocytic lymphohistiocytosis (HLH) in adults is most commonly due to acquired factors and an underlying infection is the culprit in a significant proportion of cases.
- Meticulous search for reversible inciting factors in this cohort of patients is of paramount importance.
- Prompt institution of treatment directed towards the inciting factor is the core principle of treating secondary HLH.
- Timely institution of immune suppression aimed at taming the lethal immune cascade in those not responding to definitive treatment may be lifesaving.
- Use of immune suppression in HLH secondary to infection may appear counterproductive; however, in the case presented above, it resulted in a favourable outcome.

The treatment of HLH in principle includes eliminating any possible underlying trigger and regulating the overactive immune system. For example, if an infection or malignancy is identified, patients should be promptly started on the appropriate therapy and this may occasionally be sufficient to halt the immune dysregulation. On the other hand, in those with known genetic predisposition or EBV infection or in situations where a clear trigger is not apparent, an etoposide-based regimen should be initiated as soon as possible.[3] Disseminated histoplasmosis was the trigger in our patient and, therefore, she was started on antifungal therapy. However, for those with HLH due to an inciting factor, additional treatment with immunosuppressive agents should be commenced immediately in severe cases with inadequate response to 2–3 days of disease-specific treatment.[3] In our patient, when 4 days of appropriate antifungal therapy did not lead to clinical improvement, we decided to add immunosuppression with dexamethasone and etoposide in an effort to halt the immune cascade. This led to a dramatic improvement in the patient's clinical status and subsequent withdrawal of immunosuppression while continuing the definitive treatment (antifungals) directed at the cause (disseminated histoplasmosis).

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Contributors All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content of the manuscript. Specific contributions made by each author are listed below. SRKS: conception of the idea and design, obtaining consent from the patient and drafting the manuscript. KT and SRKS: literature review and analysis. KT and VD: revising the manuscript critically for errors and important intellectual content. VD: approval of the version of the manuscript to be published.

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REFERENCES

1 Otrock ZK, Eby CS. Clinical characteristics, prognostic factors, and outcomes of adult patients with hemophagocytic lymphohistiocytosis. *Am J Hematol* 2015;90:220–4.
2 Rouphael NG, Talati NJ, Vaughan C, *et al*. Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007;7:814–22.
3 Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. *Blood* 2015;125:2908–14.
4 Henter J-I, Horne A, Aricó M, *et al*. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007;48:124–31.
5 Henter J-I, Samuelsson-Horne A, Aricò M, *et al*. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. *Blood* 2002;100:2367–73.
6 Rivière S, Galicier L, Coppo P, *et al*. Reactive hemophagocytic syndrome in adults: a retrospective analysis of 162 patients. *Am J Med* 2014;127:1118–25.
7 Parikh SA, Kapoor P, Letendre L, *et al*. Prognostic factors and outcomes of adults with hemophagocytic lymphohistiocytosis. *Mayo Clin Proc* 2014;89:484–92.
8 Salmon-Ceron D, Tubach F, Lortholary O, *et al*. Drug-Specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French ratio registry. *Ann Rheum Dis* 2011;70:616–23.
9 Wallis RS, Broder M, Wong J, *et al*. Reactivation of latent granulomatous infections by infliximab. *Clin Infect Dis* 2005;41 Suppl 3:S194–8.
10 Ferguson-Paul K, Mangum S, Porter A, *et al*. Hemophagocytic lymphohistiocytosis and progressive disseminated histoplasmosis. *Emerg Infect Dis* 2016;22:1119–21.
11 Subedee A, Van Sickels N. Hemophagocytic syndrome in the setting of AIDS and disseminated histoplasmosis: case report and a review of literature. *J Int Assoc Provid AIDS Care* 2015;14:391–7.
12 Townsend JL, Shanbhag S, Hancock J, *et al*. Histoplasmosis-induced hemophagocytic syndrome: a case series and review of the literature. *Open Forum Infect Dis* 2015;2:ofv055.
13 Ocon AJ, Bhatt BD, Miller C, *et al*. Safe usage of anakinra and dexamethasone to treat refractory hemophagocytic lymphohistiocytosis secondary to acute disseminated histoplasmosis in a patient with HIV/AIDS. *BMJ Case Rep* 2017;30:bcr2017221264.