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Adult hemophagocytic lymphohistiocytosis; the insidious assassin

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Abstract

We present a case of a 60 year-old male who presented with fever and abdominal pain along with pancytopenia and elevated ferritin level. He was diagnosed with Epstein Barr virus (EBV) related hemophagocytic lymphohistiocytosis (HLH) and subsequently treated with dexamethasone and later in his clinical course with rituximab. Unfortunately the patient suffered a motor vehicle accident and as a result had a splenectomy but relapsed shortly thereafter and expired. As the patient himself declined treatment with etoposide, this is a case of EBV induced HLH which was treated with dexamethasone and rituximab alone. We discuss the importance of prompt recognition and treatment options as well as future directions in therapy currently being investigated.

Keywords

hemophagocytic lymphohistiocytosis; epstein barr virus; rituximab

Introduction

Hemophagocytic lymphohistocytosis (HLH) is a rare, aggressive disease of the immune system. It primarily affects infants but also affects older children and adults. The exact incidence of HLH in adults is unknown but the number of reports is on the rise, which could be attributed to clinical vigilance [1].

Primary HLH is caused by genetic malfunction of the T lymphocytes and NK cells. Adult HLH is usually secondary to infections, malignancies, or rheumatologic conditions but could be unassociated with any underlying medical diagnosis [2]. In this case, we summarize the clinical course of an adult patient with HLH and discuss updates on the management of this disease.

Case Presentation

This is a 60 year-old male with a past medical history of hypertension who presented with several week history of recurrent fever accompanied by poorly localized abdominal pain. His physical examination revealed an acutely ill-appearing man with tender hepatosplenomegaly. Routine laboratory workup revealed pancytopenia, transaminitis as well as elevated alkaline phosphatase (1,641u/L) and hyperbilirubinemia (total bilirubin 3.3mg/dL). His LDH was 969 u/L and GGT was 346 u/L. In addition, aPT was 14.8 seconds, aPTT was 38.6 seconds, INR 1.3, albumin 2.7 g/dL, and triglycerides were 233 mg/dL. His initial ferritin level was 16,000 (normal range 20-380)ng/mL raising the suspicion for HLH. Subsequently, a bone marrow biopsy and aspiration was obtained which noted hypercellularity with

increased trilineage hematopoiesis and the presence of occasional hemophagocytic cells (figure 1). A soluble CD25 (sIL2 receptor) level, which is highly specific in this context, was markedly elevated at 45,580 (normal 400-1100) U/mL. The above findings satisfied six of the eight diagnostic criteria of HLH (shown in table 1). The patient was started on dexamethasone at 10mg/m2. The role of etoposide was discussed but not given per the patient's wishes.

Given the lack of family history of HLH and the late onset of presentation, genetic testing was not pursued. Secondary causes of HLH were considered and he was found to have recent Epstein Barr virus (EBV) infection, a possible inducer of HLH. His EBV IGM antibody was elevated at 2.55 (positive if >1.10) going down to undetectable 4 days after initiation of dexamethasone. EBV IgG was 2.7 (positive if >1.10) with subsequent decrease to 2.13. He initially had a positive EBV nuclear antigen (EBNA)>5.0. The pattern was most consistent with a recent EBV infection. His EBV DNA PCR quantitative results were in fact less than 200 but the test was run four days after initial presentation and empiric initiation of dexamethasone had already been started at the time of the blood draw.

Additional laboratory workup included ANA, rheumatoid factor, viral hepatitis panel and HIV, VZV, HSV, adenovirus and parvovirus B19, which were unremarkable. The flow cytometry of the peripheral blood and bone marrow biopsy revealed no monoclonal lymphoid or plasma cell population. Blood smear examination and serology were negative for Ehrlichiosis or Babesiosis.

A CT scans of the chest, abdomen and pelvis were negative for occult malignancy.

The ferritin, liver enzymes and most of the parameters improved rather quickly with the use of corticosteroids. His EBNA also became undetectable.

Three weeks after initiation of dexamethasone, rituximab at 375mg/m^2 was initiated owing to persistent thrombocytopenia (platelet count of 22x10^3/µL), which was continued at once a week for 4 weeks. This resulted in a transient improvement of his platelet count, which stabilized between 37x10^3/µL and 50x10^3/µL. He had both laboratory and clinical response thereafter and eventually his dexamethasone was tapered slowly.

His course was complicated by a motor vehicle accident, which resulted in a ruptured spleen with resultant splenectomy. A biopsy of the spleen showed increased macrophages. His thrombocytopenia improved post-operatively but upon discontinuation of the dexamethasone the patient relapsed with multi-organ failure and expired shortly thereafter. The clinical course is shown in table 2.

Discussion

Viral infection is a common cause of secondary HLH, including cytomegalovirus, parvovirus, herpes simplex virus, varicella zoster virus, influenza and most prominently Epstein Barr virus [3]. In regards to primary HLH, there are five subtypes of genetic mutations which indicate familial HLH. The mutations which should be tested for are as follows:

Genetic HLH	Gene	Protein	Chromosome location
FHL-1	HPLH1	Unknown	9q21.3–q22
FHL-2	PRF-1	Perforin	10q22
FHL-3	UNC13D	Munc13–4	17q25.3
FHL-4	STX11	Syntaxin 11	6q24.1
FHL-5	STXBP2(UNC18B)	MUNC18–2	19p13.3-p13.2

Although generally genetic testing is indicated in all patients who meet diagnostic criteria for HLH, the decision to forego genetic testing in our patient was based on the lack of a family history and the late onset of his presentation [5].

There have also been case reports of dengue induced HLH. Although rare, bacterial causes of HLH do occur. Other causes include malignancies and autoimmune disorders [4]. Mortality rate in secondary HLH has been reported to vary between 8-24% and could be worse in malignancy-related cases [4].

Treatment of secondary HLH is designed to target the underlying cause when identified. For example, if malignancy is found, specific cancer therapy should be immediately begun [6]. There are reported cases of secondary HLH treated with corticosteroids alone as well as one case of Epstein Barr induced HLH that was successfully treated with rituximab alone [7].

There are no prospective trials to guide treatment of HLH in adults. A common approach of treatment is based on the HLH-94 protocol and includes the use of an 8-week induction protocol of etoposide at 150mg/m^2 as well as dexamethasone dosed at 10mg/m^2 [1]. Patients with neurologic symptoms additionally receive intrathecal methotrexate and hydrocortisone therapy. In this pediatric-based protocol, patients with familial or recurrent conditions were further treated with alemtuzumab (CD52 monoclonal antibody) and allogeneic stem cell transplantation. As the regimen was associated with many early relapses, a revised protocol, HLH-2004 incorporates cyclosporine dosed at 6mg/kg daily divided in two doses for a target blood level of 200 mg/L but is not widely used [8]. Having possible limitations and toxicities in use of etoposide in mind, it may be reasonable in the appropriate clinical setting to forgo treatment with etoposide. This may be the case in patients who have known underlying triggers such as our patient with suspected EBV, especially those who are not critically ill and are relatively stable. Alternative treatment options utilizing rituximab may be considered as successful therapy of EBV-induced HLH have been reported.

For induction therapy purposes in patients who are more severely ill etoposide, in conjunction with dexamethasone, is dosed 150mg/m^2 to be given twice weekly for the first two weeks then weekly for the remainder of the total 8 week induction course. Only in cases where the ANC is < 0.5 x 10^9/L and if the bone marrow is hypo-cellular could one consider the removal of the first two doses in the induction protocol. This was a noted change in the HLH-94 protocol owing to a marked number of patients requiring a decrease in the etoposide dosing regimen secondary to severe cytopenia and immune deficiencies. Otherwise, a dose reduction to 5mg/kg is considered in patients who have a weight less than 10kg.

As mentioned above, cyclosporine is included in the HLH-2004 induction protocol. Cyclosporine was used in the HLH-94 protocol if patients had familial disease or relapsing disease. According to their findings, the regimen including etoposide, dexamethasone plus cyclosporine resulted in improved outcomes but there were significant numbers of early relapses. These findings prompted the addition ofcyclosporine to the induction protocol in the HLH-2004 guidelines. There are limitations to its use including renal impairment as well as reported cases of posterior reversible encephalopathy syndrome which already can be present as part of the clinical presentation of HLH [8].

Our patient initially responded to dexamethasone alone, but eventually with his persistent thrombocytopenia the choice to add an additional agent was made. It was discussed with the patient the need and role of etoposide but as the patient had expressed a desire to forgo treatment with etoposide, rituximab was included in his treatment course. EBV does not routinely respond to antivirals. The virus resides primarily in the B-lymphocytes [3]. Rituximab has been shown to be effective in eliminating EBV infected B-cells. This decreases the load of the causative pathogen, i.e. EBV, which turns down the hyperactive immune response triggered by the infection. Rituximab has been studied as a potential treatment option for EBV induced HLH in conjunction with etoposide, dexamethasone and/or cyclosporin. Of note, several of these patients in this study also received IVIG, retroviral medications and some underwent allogenic stem cell transplantation. Our patient initially had evidence of at least recent EBV infection with an elevated EBV IGM of 2.25 and IGG of 2.7. His EBV viral load was measured four days after empiric initiation of dexamethasone therapy and was less than 200 at that time. Considering the response to treatment he had including his decline in IGM from 2.25 to undetectable 4 days after initiation dexamethasone therapy it is reasonable to presume EBV was the causative agent for his lymphoproliferative disorder. Rituximab is considered first line therapy by some for EBV induced HLH, but an indication would be a viral load of greater than 10,000 copies at initial presentation. Considering his clinical decline as discussed above, rituximab was offered to the patient and he subsequently responded but ultimately succumbed to his diagnosis.

Immediate improvement in the signs and symptoms of HLH was reported in 43% of patients treated with the addition of rituximab. A significant drop in the viral load of EBV was noted in 73% of patients with those achieving levels within normal range or undetectable.

An improvement in survival was also noted in the study and thus rituximab has been deemed a potential beneficial treatment option for patients diagnosed with EBV induced HLH [3].

Newer direction focuses on the use of tocilizumab, a potent IL6 blocking monoclonal antibody [9]. A clinical trial is currently underway to test the effectiveness of this cytotoxic-sparing approach (NCT02007239).

Hemophagocytic lymphohistiocytosisis a disease with high mortality that is estimated to be 50% [10]. Prompt recognition and diagnosis of the disease, including comprehensive workup for underlying causes allow early intervention and incorporation of multi-agent regimens including stem cell transplant that can result in long-term survival and cure.

Tables

Table 1: Diagnostic criteria for HLH, patient should meet at least five out of eight.

1) Fever >38.5 C
2) Cytopenia, at least two: hemoglobin<9g/dL, ANC <1.0x10^3/μL, Platelets <100x10^3/μL
3) Splenomegaly
4) Fasting triglycerides >265 mg/dL or fibrinogen <150 mg/dL
5) Hemophagocytosis on bone marrow, liver, spleen or nodes
6) Ferritin > 500 ng/mL
7) Two standard deviation elevation of soluble CD25 (IL2 receptor)
8) Low or absent NK cell activity

Table 2

	WBC	Hgb	PL	Ferritin	Bilirubin	AST	ALT	AlkPhos	Intervention
Initial	2.7	8.9	34	>16500	3.3	177	110	1649	Dexamethasone 10 mg/m2 daily on day 4
Week 1	9.2	10.5	103	2264	1.3	75	70	1365	Dexamethasone 8 mg/m2 daily
Week 3	4.6	9.3	22	3014	1.3	44	74	397	Rituximab 375 mg/m2 weekly x4 added
Week 8	7.7	10.6	139	1653	0.9	46	83	282	Dexamethasone 4 mg/m2 daily then step-wise slow taper
Week 17	5.0	11	103	>16500	9.2	310	344	2110	ICU stay then death

Abbreviations and units: WBC white blood cells, x10^3/μL; Hgb hemoglobin g/dL, PL platelets x10^3/μL; ferritin ng/mL; bilirubin mg/dL; AST aspartate aminotransferase U/L; ALT alanine aminotransferase U/L; alkphos alkaline phosphatase U/L.

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