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Haemophagocytic Lympho-Histiocytosis associated with 2 cases of pediatric lymphocyte-depleted classical Hodgkin lymphoma

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal syndrome of abnormal T-cell activation and cytokine production, which can be familial or secondary in nature. Although HLH can occur concomitantly with lymphomas, the development of HLH alongside Hodgkin lymphoma in children is unusual. Here we report the diagnostic evaluation and clinical course of 2 paediatric cases of HLH secondary to lymphocyte-depleted classical Hodgkin lymphoma. These cases highlight the need to be vigilant for this rare presentation and the difficulties in managing these patients.

Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare and often fatal syndrome of hyperinflammation characterized by excessive activation of haemophagocytic macrophages, cytotoxic T-cells and natural killer (NK) cells. The resulting immune dysfunction leads to cytopenias, fever, hepatosplenomegaly and a down-regulation of the immune response¹. HLH exists in two forms, either as a primary hereditary disease or as a secondary acquired condition¹.

The hereditary variant of HLH usually occurs in infancy but later presentation throughout childhood and young adulthood has been reported^{2,3}. A variety of distinct genetic disorders and specific gene mutations including PRF1, UNC13D, STX11, and STXBP, have been described in hereditary HLH⁴⁻⁷. These genes are important in controlling the exocytosis of cytotoxic granules, essential for normal natural killer (NK) cell and cytotoxic T-cell function^{8,9}. In contrast, infection, malignancies, autoimmune disorders and immune deficiency syndromes can trigger secondary or acquired HLH.

Epstein Barr virus (EBV) is the most frequently described viral trigger of HLH. EBV is predominantly a B lymphotropic human γ -herpesvirus¹⁰. However, rarely infection of NK and T cells has been observed and this is strongly associated with EBV-associated HLH¹¹. Malignancy-associated HLH can be triggered by either the malignancy itself or following chemotherapy. T and NK cell lymphomas are the most frequently HLH-associated malignancies and also highly associated with EBV infection¹². Although secondary HLH is uncommon in B cell lymphomas there are numerous case reports describing an association with Hodgkin lymphoma (HL)¹³⁻¹⁶.

HL exists as two distinct clinical entities: classical HL (cHL) and nodular lymphocyte predominant HL (NLPHL). The 2008 WHO classification further subdivides cHL into four subtypes; nodular sclerosis, mixed cellularity, lymphocyte-rich and lymphocyte-depleted classical Hodgkin lymphoma (LDCHL)¹⁷. EBV is implicated in the aetiology of HL with the degree of EBV association varying across subtypes. EBV onco-proteins are detectable in the Hodgkin Reed Sternberg (HRS) cells of LDCHL in over 90% of cases¹⁷. LDCHL is the rarest cHL subtype accounting for 1-5% of newly diagnosed cHL in western countries. There is a male preponderance with the median age at presentation between 30-37 years^{17,18}. Although LDCHL can occur in the paediatric population it is extremely scarce. The UK based paediatric HD3 trial reported no cases of LDCHL¹⁹. Similarly only 16 cases are recorded in the SEER database (2002-2011)²⁰. As a consequence of its rarity, definitive histopathological identification is often difficult and clinical characteristics, course and outcomes of paediatric patients with LDCHL is poorly understood.

Due to the challenge of distinguishing HLH from other entities such as malignancy and infection determining underlying aetiology is difficult. Here, we report two cases of LDCHL occurring in childhood, complicated by developing HLH soon after initial presentation and commencement of chemotherapy. Literature describing childhood LDCHL-associated HLH is lacking and treatment recommendations for these children need to be determined. We

discuss our experience of managing this distinct condition resulting from co-occurrence of two rare entities.

Observations

Case 1

A previously fit and well five-year-old white Caucasian girl presented with a 4-week history of fever, lethargy and weight loss. At presentation, her haemoglobin measured 75 g/l, total white cell count $3.0 \times 10^9/l$ (neutrophil count 1.8) and platelet count $53 \times 10^9/l$. On examination she looked well but pale with a palpable spleen measuring 5 cm below the costal margin. Several diagnostic investigations were undertaken including a bone marrow aspirate which revealed no evidence of malignant infiltration or haemophagocytosis but mild dysplasia. Although the monospot screen for infectious mononucleosis was negative, EBV PCR on serum demonstrated 9192 copies/ml. She was also noted to have a normal triglyceride level of 1.25mmol/L but an elevated serum ferritin of 902 $\mu\text{g/l}$ (Figure 1).

She received broad-spectrum antibiotics, piperacillin/tazobactam, but continued to be febrile. Although no infectious agent was identified, her antibiotics were empirically changed to meropenem. Over the course of a week, she developed tender hepatomegaly and mild splenic enlargement. Causes of primary liver failure were excluded.

Further exploratory work-up included a CT neck-thorax-abdomen scan, which showed extensive lymphadenopathy prompting a lymph node biopsy. Pathology review reported total effacement of lymph node architecture by Hodgkin cells within a background of depleted lymphocytes and an increased number of histiocytes but no evidence of haemophagocytosis. The malignant cells co-expressed CD15, CD30 and PAX5, classical immune-phenotypic markers of cHL and were EBER positive indicating EBV within the tumour. Thus the morphology and immunohistochemical analysis were consistent with a diagnosis of LDCHL. Further, lack of reactivity to CD20, CD3, CD8, CD4, CD43, CD2, CD5, CD45, EMA and ALK differentiated it from ALK negative anaplastic large cell lymphoma.

The patient commenced prednisolone as part of OEPA (vincristine, etoposide, prednisolone and doxorubicin) induction regime for HL (EuroNet-PHL-C1, NCT00433459). Within 48hrs, she became significantly fluid overloaded, developed an oxygen requirement and acute respiratory distress. In view of progressive clinical deterioration, her steroids were switched to dexamethasone. A diagnosis of secondary HLH was made based on fever, splenomegaly, cytopenia, and elevated ferritin (Table 1)²¹. Although measurement of sCD25 was performed and showed marked elevation at 44736U/ml, this result was not available till after the clinical decision was made. In addition to sCD25, cytokine profiling showed significant derangement (Table 2). Immunosuppressive therapy was initiated and she received three doses of etoposide 125mg/m² and cyclosporine, in accordance with the HLH-2004 protocol, NCT00426101).

Despite changing therapy to treat HLH she continued to decline, developing tense ascites and disseminated intravascular coagulation. Her jaundice worsened with a marked conjugated

hyperbilirubinaemia and a liver biopsy was done to aid diagnosis. The biopsy revealed scattered atypical cells and although not identified morphologically as classical Hodgkin Reed- Sternberg cells were strongly EBER positive and expressed CD15, CD30 and PAX5.

Her clinical condition deteriorated rapidly over the next 24 hours leading to admission to the paediatric intensive care unit (PICU). There was no evidence of profound post-biopsy bleed, although she had significant coagulopathy and thrombocytopenia. She developed intractable hypotension and severe metabolic acidosis secondary to multi-organ dysfunction. Sadly, she died 30 days after initial presentation to our hospital.

Case 2

A fourteen-year-old boy of Pakistani origin presented to his local hospital with fever, jaundice, anaemia and lymphadenopathy. Prior to this he had been well but known to be glucose-6-phosphate dehydrogenase deficient with mild eczema and asthma. In other history of note, he recently travelled to Pakistan during which time he had been unwell with reports of a viral gastroenteritis. He was referred to the liver unit for investigation of his jaundice. Clinical examination confirmed jaundice and lymphadenopathy; in addition he had ascites, hepatosplenomegaly and a left-sided pleural effusion. Chest X-ray confirmed the pleural effusion and ultrasound imaging detected a liver lesion. Laboratory analysis indicated a pancytopenia, poor renal function and an elevated lactate dehydrogenase of 1110 IU/L. He was also IgG positive for Hepatitis A, consistent with a past infection.

Within hours of presenting, he developed hypovolemic shock, worsening abdominal distension due to the ascites and fulminant respiratory failure resulting in admission to PICU. He required inotropic support for 5 days while his condition stabilized. Although febrile, blood cultures at presentation were negative with no infectious agent identified. He was empirically commenced on dexamethasone 6mg/m²/day, on suspicion there was an underlying malignant process. A bone marrow aspirate/trephine performed revealed multifocal infiltration of inter-trabecular spaces by EBER positive atypical cells co-expressing CD30 and PAX5 and an increased numbers of CD68 and CD163 positive macrophages were detected.

Consistent with his bone marrow findings a lymph node biopsy revealed features suggestive of LDCHL. The neoplastic cells were positive for CD30, CD15, PAX5 and EBER and no reactivity for CD20, CD3, CD45, CD8, CD4, EMA, ALK, BCL-2 or CD10. He commenced OEPA induction regime for HL (EuroNet-PHL). However, this was changed to HLH-2004 protocol the following day once his serum ferritin (8276 U/ml) and sCD25 (30624 U/ml) were known. He fulfilled 6 of 8 criteria required for diagnosis of HLH: fever, splenomegaly, cytopenia, hypertriglyceridemia (4.21mmol/L), elevated ferritin and sCD25 (Table 1 and Figure 2)²¹. Further supporting the diagnosis of HLH, his cytokine profile was abnormal (IL-10 680 pg/ml, IL-6 115 pg/ml, TNF- α 130 pg/ml) (Table 2). His EBV PCR on admission was 6104 copies/ml, which had risen to 39265 copies/ml before he commenced the HLH-2004 protocol.

He continued to need PICU support for his multi-organ failure and coagulopathy. Over the following week he appeared to stabilise and made sufficient improvement that he returned to the main ward. A clinical decision was made to add rituximab to his treatment regime, which he tolerated well. Despite an apparent response to his treatment with a fall in his serum ferritin, he succumbed to sepsis and died 35 days after admission. Both candida and enterococcus were isolated in extended blood cultures.

Discussion

Malignancy-associated HLH is well described in the paediatric population but to our knowledge this is the first report of paediatric LDCHL-associated HLH. Across 3 recent retrospective studies of malignancy-associated HLH in children and adolescents, only 4 out of a total of 72 patients were documented to have cHL-associated HLH (2 nodular sclerosis, 1 lymphocyte-predominant, 1 subtype not specified)²²⁻²⁴. This is possibly, in part, due to the rarity of LDCHL in children. There are only limited clinical descriptions of children with LDCHL in the literature. In adults, LDCHL compared with other HL subtypes, present more frequently with unfavourable characteristics such as advanced stage, involvement of bone marrow and liver and B symptoms. A small study of 310 adult patients, 29 were LDCHL and these patients had an inferior outcome, five-year overall survival: 29% vs. 86% ($P < 0.001$)¹². A much larger German series of 10,019 adult patients identified 84 patients with LDCHL and reported 5 years OS, 83% v 92% ($p = 0.0018$) in LDCHL compared with patients with other HL subtypes¹⁸.

A delay in recognition of lymphoma-associated HLH is not uncommon as HLH manifestations may be indiscernible from the lymphoma or HLH precedes the diagnosis of malignancy. Furthermore, in secondary HLH pathognomonic haemophagocytosis may not be seen until the disease progresses. However, abnormal serum ferritin, triglyceride and fibrinogen levels should raise suspicion and prompt measurement of sCD25. In an analysis of sCD25 in cHL subtypes without evidence of HLH, patients with LDCHL had significantly higher sCD25 (median: 8240 U/ml in LDCHL patients compared to 1705 U/ml in non-LDCHL patients)¹². Interestingly, both patients reported here had exceedingly high sCD25, more than 10-fold above the minimum level for diagnosis of HLH. Such high sCD25 levels may serve, as a useful indicator that a patient with LDCHL is atypical and complicated by concomitant HLH. Similarly, although serum ferritin is non-specifically raised in many inflammatory conditions, in paediatric patients, high levels are most commonly associated with HLH²⁵. Notably, the second patient presented with a higher ferritin compared to the first patient, possibly correlating with the severity of HLH, hence rapid clinical progression and onset of HLH seen.

Rituximab, a monoclonal antibody to CD20, is standard therapy to treat many B-cell malignancies^{26,27}. However, HRS cells despite their B cell origin do not express typical B-cell lineage markers including CD20²⁸. We opted to add rituximab to the treatment for Case 2 as; 1) rituximab has been reported to be effective in EBV associated HLH²⁹ and 2) rituximab may also have therapeutic value in patients with cHL^{30,31}. In cHL, rituximab is hypothesized to work by either depleting reactive B lymphocytes from the microenvironment, which may

enhance antitumor immunity, or by killing the putative CD20-expressing HL stem cells. However as rituximab does not deplete the T cell or NK cell pool it is unlikely to be effective as a single agent.

HLH is often refractory to therapy and carries a high mortality rate. In the paediatric population, there is little evidence-based medicine to guide clinical decisions in the management of refractory malignancy-associated HLH and none for LDCHL-associated HLH. Salvage strategies from individual case reports aim to either, control the cytokine storm by removal of cytokines via plasmapheresis³² or use targeted therapies against immune cell subsets. Both our patients were haemodynamically unstable with coagulopathy making plasmapheresis a risky procedure for uncertain benefit.

Daclizumab, a monoclonal antibody against CD25 has been used with success in paediatric-HLH on an individual basis³³. In this case daclizumab was administered alongside other cytotoxic and immunosuppressive agents making it difficult to determine which drug was responsible for the observed clinical improvement. However, given the extremely high levels of soluble CD25 in our patients it is possible that daclizumab could have proven useful. CD25 is also an attractive target in cHL as it is expressed in both a minority of HRS³⁴ cells but also on regulatory T cell, abundant in the tumour microenvironment³⁵. Anti-CD25 drug conjugates have been trialled in refractory/relapsed Hodgkin with evidence of activity^{36,37}. However, daclizumab has been withdrawn from the market following a number of patients with multiple sclerosis developing immune-mediated encephalitis after receiving the drug³⁸.

A second monoclonal antibody, alemtuzumab that targets CD52 on lymphocytes, monocytes, macrophages and dendritic cells has been also tested³⁹. The primary indication of alemtuzumab is in the treatment of chronic lymphocytic leukaemia⁴⁰ and multiple sclerosis^{41,42}. However, a retrospective study of alemtuzumab use in 22 paediatric and adult patients with refractory HLH found at least 64% had some improvement³⁹. Patients had a received variety of therapies before initiation of alemtuzumab, which was given in a range of dosing schedules. The most significant complication in that study was high incidence of viremias following alemtuzumab, in particular reactivation of cytomegalovirus³⁹. The high EBV viral load of our patients made us cautious against alemtuzumab.

A number of reports also suggested targeting inflammation by blocking the tumor necrosis factor (TNF) axis using either infliximab an anti-TNF-alpha monoclonal antibody or the TNF inhibitor, etanercept⁴³. These agents are used to treat inflammatory bowel disease and historically clinicians were concerned with the risk of developing lymphoma and HLH in patients who received such therapy. However, a large prospective study of 5766 patients 17-years old or younger found no increased risk of HLH associated with infliximab⁴⁴. Infliximab certainly warrants further study in the context refractory paediatric-HLH.

A delay in the diagnosis of HLH often proves to be catastrophic and it is important for clinicians to be alert to its possibility. The two children at our centre showed rapid deterioration and were in extremis at the point of commencement of immunosuppressive therapy. The triad of lymphoma, high EBV load and HLH in our patients posed a number of

challenges from diagnosis to therapeutic management. A lack of prospective, randomized or controlled clinical trials in malignancy-associated HLH makes it difficult to determine whether an HLH-directed, malignancy-directed or combined approach should be adopted. Although the treatment regimes do often overlap for example etoposide used in induction chemotherapy for cHL is also proven to be beneficial in EBV-associated HLH as well as part of HLH-2004 protocol. However, the best therapeutic options in refractory-HLH still need to be determined for children and adults alike.

Table 1 Diagnostic criteria for HLH²¹

The diagnosis HLH can be established if one of either 1 or 2 below is fulfilled	
1	A molecular diagnosis consistent with HLH
2	Diagnostic criteria for HLH fulfilled (five out of the eight criteria below)
	Fever (peak temperature of > 38.5° C for > 7 days)
	Splenomegaly (spleen palpable > 3 cm below costal margin)
	Cytopenia involving > 2 cell lines (Hb < 9 g/dL, absolute neutrophil count < 100/μL, platelets < 100,000/μL)
	Hypertriglyceridemia (fasting triglycerides > 2.0 mmol/L or > 3 standard deviations [SD] more than normal value for age) or hypofibrinogenemia (fibrinogen < 1.5 g/L or > 3 SD less than normal value for age)
	Hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes)
	Low or absent natural killer cell activity
	Serum ferritin > 500 μg/L
	Elevated soluble interleukin-2 (CD25) levels (>2400 U/mL or very high for age)

Table 2 Summary of cytokine profile

Cytokine and sCD25	Case 1	Case 2	Reference
sCD25 U/ml	44736	30624	200-500
IL-10 pg/ml	10000	680	<3
IL-1β pg/ml	19.8	10.5	<5
IL-6 pg/ml	346	115	<6
IL-8 pg/ml	64.5	5.66	<70
TNF-a pg/ml	60.8	130	<3
EPO mU/ml	7.49	40	<30

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Figure Legends

Figure 1: Schematic showing the serum concentrations of bilirubin, triglyceride and ferritin, as well as the EBV copy number in Case 1, alongside treatment.

Figure 2: Schematic showing the serum concentrations of bilirubin, triglyceride, ferritin and sCD25, as well as the EBV copy number in Case 2, alongside treatment.