Acute liver dysfunction as a presentation of haemophagocytic lymphohistiocytosis

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Abstract

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon disorder of histiocyte function which presents with fever, cytopaenias and end-organ dysfunction. We report the case of a 62-year-old man with acute liver dysfunction as an initial presentation of HLH.

Haemophagocytic lymphohistiocytosis (HLH) is characterised by excessive macrophage activation resulting in multiple organ damage. It should be considered in patients with pyrexia of unknown aetiology, cytopaenias and evidence of end-organ (especially liver) dysfunction.

Case report

A 62-year-old gentleman with ulcerative colitis diagnosed at age 31 (quiescent and not on treatment at time of presentation) and Barrett’s oesophagus presented with 2 months of fever, fatigue and weight loss. His liver edge was 2 cm below the costal margin, with no lymphadenopathy or splenomegaly.

Over 4 weeks he had developed marked liver dysfunction (albumin 21 g/L; INR 1.3; bilirubin 95 µmol/L; ALP 283 U/L; GGT 358 U/L; ALT 62 U/L; AST 134 U/L) and pancytopenia. Ferritin, triglycerides, vitamin B12 and folate were initially normal.

Initial bone marrow aspirate and trephine examination showed a normocellular bone marrow with infrequent haemophagocytosis. Autoimmune screen (antinuclear antibody, rheumatoid factor, anti-CCP, anti-Ro, anti-La, smooth muscle antibodies, parietal cell antibodies and antimitochondrial antibodies) was unremarkable apart from a positive antinuclear cytoplasmic antibody (ANCA) (normal MPO and PR3 levels). EBV, CMV and hepatitis A, B and C were negative.

Abdominal ultrasound and magnetic resonance cholangio-pancreatography were unremarkable. CT abdomen showed no lymphadenopathy or intra-abdominal malignancy.

Given progressive liver dysfunction and cytopaenias, bone marrow aspirate and trephine biopsy were repeated 2 weeks after the initial biopsy, this time showing haemophagocytosis (Figures 1 & 2).

Liver biopsy revealed sinusoidal congestion with haemophagocytosis (Figure 3). Ferritin was now 1047 µg/L (2–500 µg/L) and triglycerides were elevated (6.1 mmol/L), thus fulfilling the HLH-2004 diagnostic criteria.
Treatment was started according to the HLH-2004 protocol (dexamethasone, cyclosporin, etoposide and intrathecal methotrexate) resulting in normalisation of all parameters. The patient is now asymptomatic and off treatment 18 months after diagnosis.

Figure 1. May-Grunwald-Giemsa stain of bone marrow aspirate showing red cell (red arrow) phagocytosis by a macrophage (black arrow). Magnification: 200×

Figure 2. Haematoxylin & Eosin stain of liver biopsy showing macrophages ingesting red cells (black arrows). Magnification: 200×
Discussion

HLH is a histiocytic disorder characterised by an inappropriate response to antigens. Incidence is estimated at 1.2 cases per million per year. Pathophysiology involves defective perforin-mediated cytotoxic pathways of CD8+ and Natural Killer (NK) cells.

Inability of these cells to eliminate antigens and provide negative feedback causes uncontrolled proliferation of T cells and macrophages resulting in a cytokine storm accounting for the clinical presentation.

HLH has both primary (genetic disorders in the perforin-mediated cytotoxic pathways) and secondary (no identifiable genetic predisposition) forms, which are triggered in susceptible individuals by infections, autoimmune conditions and malignancies. Primary forms almost always present before 1 year of age and without treatment are universally fatal.

Lymphohistiocytic proliferation can occur in any organ, with the liver being most commonly affected organ. The diagnosis should be considered in any patients presenting with liver dysfunction with other suggestive features. Fever, cytopaenias and hepatosplenomegaly are the cardinal features of HLH. Characteristic laboratory findings include bi- or pancytopenia, elevated ferritin, triglycerides, bilirubin, transaminases and low fibrinogen, but as seen in our case, these may be normal in early stages.

Fever is caused by high levels of interleukin (IL)-1, interleukin (IL)-6 and tumour necrosis factor (TNF)-alpha. Cytopaenias are attributed to both haemophagocytosis...
and high concentrations of TNF-alpha and interferon (IFN)-gamma. Increased levels of TNF-alpha downregulates lipoprotein lipase resulting in hypertriglyceridaemia.

The characteristically high ferritin is a result of secretion by activated macrophages, but may be normal in early presentations. Hepatosplenomegaly, liver dysfunction and CNS signs are attributed to end-organ infiltration.

Diagnosis is difficult due to the overlap of clinical features with sepsis/multi-organ dysfunction. The Histiocyte Society has produced the HLH-2004 criteria but these are not 100% specific. A ferritin level over 10,000µg/L and elevated serum CD25 are relatively specific markers for the condition.

Once diagnosed, testing for underlying genetic mutations (in the case of primary HLH-usually in infancy) and for secondary causes of the disorder (in adult presentations) should be considered.

Therapy consists of immunosupression and/or chemotherapy to control the activated macrophages and lymphocytes. Most centres follow the HLH-2004 protocol which involves high dose dexamethasone, etoposide and cyclosporine A ± intrathecal methotrexate. Patients with primary HLH will relapse following this treatment and need to proceed to haematopoietic stem cell transplant (HSCT) to achieve cure.

Patients with secondary HLH should be followed closely looking for relapse. Relapsed HLH should be considered for HSCT or further immunosuppressive treatment (the exact nature of which remains a matter of considerable debate).

**Conclusion**

HLH is an uncommon disease caused by a dysfunctional hyperactive immune response to antigens in predisposed individuals. Presenting features include fevers, hepatosplenomegaly and cytopaenias. The liver is most commonly affected and therefore HLH must be considered in any case of unexplained liver dysfunction.

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