Haemophagocytic lymphohistiocytosis secondary to parvovirus B19 infection: an unexpected case of multiorgan failure

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Introduction

Haemophagocytic lymphohistiocytosis forms part of the haemophagocytosis syndromes. These are a group of rare conditions which are characterised by a state of immune hyperstimulation, overproduction of cytokines and high risk of multi-organ failure (Hayden et al, 2016). Viral infections are well-known triggers for haemophagocytic lymphohistiocytosis in adults. The most common infectious trigger reported is Epstein–Barr virus but infections with parvovirus B19 have been implicated. B19 infection is a very rare cause of haemophagocytic lymphohistiocytosis. There are various therapeutic options for haemophagocytic lymphohistiocytosis but the biggest challenge with haemophagocytic syndromes is reaching a timely diagnosis so that treatment can be initiated before the patient becomes critically ill.

Case report

A previously healthy 40-year-old woman presented to the emergency department with a 3-day history of lethargy, myalgia, abdominal pain, fever, vomiting and shortness of breath.

She was alert, clinically dehydrated and jaundiced. Her heart rate was 114 beats per minute, blood pressure 85/41 mmHg, respiratory rate 25/min, temperature 102°F (38.8°C) and oxygen saturations 89% on air. She had bibasal chest crepitations and generalised abdominal tenderness without guarding. She had no rashes and neurological examination was unremarkable.

A non-contrast computed tomography of the thorax and abdomen showed patchy ground glass changes and extensive consolidations in both lower lobes.

The patient was resuscitated and admitted to the intensive care unit with a presumed diagnosis of septic shock secondary to pneumonia complicated by acute kidney failure. While on the intensive care unit she required high-flow oxygen via non-invasive ventilation at 40 litres/min, antibiotics and continuous haemodialysis.

After a few days, her renal function and inflammatory markers improved significantly. However, her platelet level dropped to $18x10^9$/litre, D-dimer was 80 000 ng/ml and international normalised ratio increased from 1.03 to 1.71. A computed tomography pulmonary angiogram was negative for pulmonary embolism. Anti-cardiolipin antibodies IgG and IgM and anti B2-glycoprotein levels were normal. Blood cultures, urine cultures, sputum cultures, methicillin-resistant *Staphylococcus aureus* swab, hepatitis screen, human immunodeficiency virus, Leptospira IgM and polymerase chain reaction, Rickettsia, *Mycoplasma pneumoniae*, Legionella, cytomegalovirus, herpes simplex virus and respiratory screen including COVID-19 were all negative.

Parvovirus polymerase chain reaction taken on admission was 259 837 copies/ml in keeping with severe parvovirus infection possibly complicated by disseminated intravascular coagulation. Her C-reactive protein level and renal function improved. However, her platelet levels continued to drop despite transfusions while clotting studies and liver tests remained highly deranged. Further investigations showed a high triglyceride level of 7.17 mmol/litre, fibrinogen of 0.81 g/litre and an extraordinarily elevated ferritin level of >16 500 ng/ml (normal range 10–291 ng/ml) (Table 1).

In the context of pancytopenia, coagulopathy, liver and renal failure, as well as very high ferritin levels, a diagnosis of parvovirus infection complicated by haemophagocytic lymphohistiocytosis was made. This was supported by elevated soluble serum IL-2 levels at 4650 pg/ml (upper limit of normal 2500 pg/ml) and a bone marrow biopsy showing increased level of plasma cells, macrophages and megakaryocytes.

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Case report (Continued)

High dose dexamethasone and intravenous immunoglobulin were given. However, the patient reported blurring of vision and developed status epilepticus. She was treated for status epilepticus and intubated. Magnetic resonance imaging of the brain showed posterior reversible encephalopathy syndrome which occurs in up to one-third of patients with haemophagocytic lymphohistiocytosis. The patient was then transferred to the haematology unit to commence induction therapy with intravenous etoposide and dexamethasone as well as intrathecal methotrexate. She is currently still under the care of the haematologists and being monitored closely for any signs of relapses.

Discussion

Haemophagocytic lymphohistiocytosis is a rare acute multiorgan disorder characterised by severe inflammation resulting from uncontrolled activation of macrophages and T cells (Mosser and Edwards, 2009). In a nationwide Japanese study by Ishii et al (2007) the reported annual incidence of adult and paediatric haemophagocytic lymphohistiocytosis is 1 per 800 000 with a mortality of 40% (Ramos-Casals et al, 2014). Clinically, haemophagocytic lymphohistiocytosis manifests as coagulopathy, pancytopenia, liver failure, neurological complications or haemophagocytosis. It can be primary or secondary to infections, malignancies, rheumatic diseases or drugs (Rosado and Kim, 2013).

Haemophagocytic lymphohistiocytosis secondary to parvovirus B19 infection is rare. Most cases are secondary to Epstein–Barr virus infection. Patients with viral-associated haemophagocytic syndrome benefit from intravenous immunoglobulin treatment as the antibodies can help to neutralise the virus (Barah et al, 2014).

Early diagnosis remains one of the biggest challenges because of the heterogenous presentation and other mimics such as sepsis. Clinically haemophagocytic lymphohistiocytosis gives rise to a sepsis-like picture with high fever, pancytopenia, liver failure and abnormal coagulation (prolonged activated partial thromboplastin time, elevated D-dimer levels and reduced fibrinogen levels). Possible neurological symptoms include headache, confusion, fits and coma. Neurological involvement is a poor prognostic marker and needs more aggressive treatment (Myung-Mi et al, 2012). Extremely high ferritin levels of over 10 000 ug/litre have been reported to have 90% sensitivity and 96% specificity for haemophagocytic lymphohistiocytosis (Allen et al, 2018). Ferritin serves as a good prognostic marker and can be used to monitor treatment response. Another biomarker linked with haemophagocytic lymphohistiocytosis is soluble IL-2 receptor

Table 1. Summary of investigations

Investigation (normal range)	Day 1	Day 15	Day 25	Day 50
Haemoglobin (12–15.5 g/dl)	7.1	7.3	8	9.8
White cell count (4.3–11.4x10^9/litre)	4.7	2.83	0.65	9.06
Platelets (142–349x10^9/litre)	30	32	23	193
Creatinine (45–84 µmol/litre)	659	105	70	63
Alanine aminotransferase (5–33 U/litre)	785	390	95	77
Total bilirubin (0–21 micromol/litre)	98.2	52.2	27.8	10.3
International normalised ratio (0.94–1.06)	1.73	1.65	1.38	0.97
D-dimer (up to 500)	21 900	>80 000	56 418	490
Fibrinogen (2–3.7 g/litre)	1.1	0.88	2.03	2.1
Activated partial thromboplastin time (0.91–1.09)	1.73	2.25	1.18	1.1
Ferritin (10–291 ng/ml)	>16 500	4557	1399	856
C-reactive protein (0–5 mg/litre)	309.6	141	20.2	6.4

Learning points

- Although parvovirus usually causes mild disease, severe complications such as haemophagocytic lymphohistiocytosis can occur.
- In patients with sepsis, consider alternative causes of multiorgan failure, especially when sepsis markers are improving.
- In the context of fever, pancytopenia, hepatosplenomegaly, hyperferritinaemia, neurological dysfunction, renal and liver failure, think of haemophagocytic lymphohistiocytosis.
- The heterogeneous presentation of haemophagocytic lymphohistiocytosis is a diagnostic challenge. Specialists including physicians, intensivists, infectious disease specialists and rheumatologists need to be familiar with this rare life-threatening complication as prompt diagnosis and treatment are the key to a successful outcome.
- Advances in understanding the pathophysiology, treatment strategies and newer treatments such as etoposide and IL-1 inhibitors in combination with dexamethasone offer a greater chance of survival if given early.

(CD25) which reflects T cell and NK cell activity (Yuan et al, 2016). The early use of the HScore to calculate a percentage probability for haemophagocytic lymphohistiocytosis can allow an earlier diagnosis (Allen et al, 2018).

Given its devastating nature, haemophagocytic lymphohistiocytosis requires timely aggressive treatment. In addition to high dose glucocorticoids, various chemotherapy regimens are available. The haematology team involved had more experience with the use of etoposide-based regimens. However, there is growing evidence in favour of using intravenous anakinra (Il-1 receptor antagonist) as first-line treatment for cytokine storm syndromes such as secondary haemophagocytic lymphohistiocytosis (Mehta et al, 2020). Interestingly, immunocompetent adults who develop secondary haemophagocytic lymphohistiocytosis may also have a genetic predisposition to develop a maladaptive inflammatory response but in contrast to paediatric haemophagocytic lymphohistiocytosis cases there are no known identifiable genetic mutations that can be tested for to date (Naymagon, 2021).

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