Case report

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Pregnancy-induced haemophagocytic lymphohistiocytosis

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Abstract

Haemophagocytic lymphohistiocytosis is an aggressive and life-threatening syndrome of excessive immune activation. It is associated with various aetiologies, including infections, collagen vascular diseases and malignancies. Pregnancy-induced immune dysregulation in genetically susceptible women may also play a critical role in haemophagocytic lymphohistiocytosis. Our case involves that of a 23-year-old pregnant woman who presented at 22 weeks gestation with tachycardia, swinging pyrexia, rigors and generalised myalgia. Refractory hypotension to intravenous fluids and rise in lactate level required admission to the intensive care unit for vasopressor support. Despite treatment with broad-spectrum antibiotics for presumed sepsis, she made little clinical improvement. Investigations for infection and rheumatological disease were unremarkable. A pronounced hyperferritinaemia, hypertriglyceridaemia and cytopenia raised the suspicion of haemophagocytic lymphohistiocytosis. Subsequent elevated CD25 levels helped establish the diagnosis. Treatment with corticosteroids and intravenous immunoglobulin provided a transient response in regard to temperature control and cardiovascular stability. The decision was made to treat her with anakinra, an interleukin-1 receptor antagonist. She responded well to this with a complete resolution of her symptoms and normalisation of her ferritin levels over the course of some weeks. Because of progressive slowing of foetal growth and abnormal umbilical artery Dopplers and cardiotocography, she eventually had an emergency caesarean section at 31 + 5 weeks. There were no foetal abnormalities.

Keywords

Pregnancy, haemophagocytosis, cytokine, pyrexia, haematology

Case presentation

A 23-year-old multiparous woman (gravid 2 para 1) presented to the emergency department at 22 weeks gestation with a four-day history of fever and coryzal symptoms. Associated symptoms included generalised myalgia, rigors and mild abdominal pain, particularly at the right upper quadrant. There was no history of recent foreign travel. Her medical history was unremarkable and she took no regular medication. Her obstetric history included an uneventful instrumental delivery of a healthy baby one year ago. On presentation, she was tachycardic at (140 beats/min), tachypnoeic (24 breaths/min) and pyrexial (39.2°C). She was otherwise normotensive (112/53 mmHg) and her oxygen saturation was normal (98% on room air). Physical examination was unremarkable with no organomegaly or lymphadenopathy and no evidence of a rash.

Chest X-ray done on admission was unremarkable and urine dipstick revealed 2+ protein and 1+ erythrocytes. Her electrocardiogram showed sinus tachycardia with no other abnormal features. Her blood results showed mild anaemia (haemoglobin 107 g/L) and thrombocytopenia (platelet count of 136×10^9/L), elevated C-reactive protein (CRP 131 mg/L) with normal kidney, liver function tests and coagulation profile (Table 1). Her arterial blood gas on room air showed a compensated metabolic acidosis with pH 7.47, PO2 of 11.71 kPa, pCO2 of 2.89 kPa, serum bicarbonate of 19.3 mmol/L, base excess of −6.3 mmol/L and lactate of 0.76 mmol/L.

She was initially treated for presumed sepsis of unknown origin with intravenous amoxicillin and cefuroxime and was admitted to the maternity high dependency unit (MHDU) for observation. On the MHDU, she became increasingly tachycardic with

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Table 1. Summary of patient blood results during her inpatient stay.

Day of admission	1	2	4	16	19	27	35
Haemoglobin (g/L)	107	81	86	69	87	78	85
White cell count ($\times 10^9$/L)	6.1	3.8	4.0	17.7	17.1	13.5	3.9
Platelets ($\times 10^9$/L)	136	95	116	321	199	300	113
C-reactive protein (mg/L)	131		208	214	50	97	7
Ferritin (ng/mL)					>40,000	27,021	8531
Cholesterol (mmol/L)				4.4	5.2		
Triglyceride (mmol/L)				6.8	9.9		
High-density lipoprotein (mmol/L)				0.7	1.1		

Table 2. Diagnostic criteria adapted from the HLH-2004 trial.

Molecular identification of an HLH-associated gene mutation (e.g. PRF1, UNC13D, STX11, STXBP2, Rab27A, SH2D1A, BIRC4, LYST, ITK, SLC7A7, XMEN, and HPS)
OR
Five of the following eight findings:

1. Fever $\geqslant 38.5^{\circ}$C
2. Splenomegaly
3. Peripheral blood cytopenia
4. Hypertriglyceridemia (fasting triglycerides >265 mg/dL) and/or hypofibrinogenaemia (fibrinogen < 150 mg/dL)
5. Haemophagocytosis in bone marrow, spleen, lymph node or liver
6. Low or absent NK cell activity
7. Ferritin > 500 ng/mL
8. Elevated soluble CD25 (soluble IL-2 receptor alpha) two standard deviations above age-adjusted laboratory-specific norms

Note: Adapted from Jordan et al.[1]

hypotensive episodes which persisted despite appropriate fluid resuscitation. At this point, she has also started to develop an erythematous macular rash around the malar area of her face, knees and elbows with a significant generalised arthralgia. With her deteriorating clinical picture, she was transferred to the ICU for vasopressor support.

Her blood tests during her stay in ICU showed a picture of progressive pancytopenia with marked elevation in CRP. Intermittent periods of pyrexia were found to be associated with hypoxemia and hypotension. This necessitated management with intermittent periods of high-flow nasal oxygen and metaraminol, respectively. On the advice of the microbiology team, her antibiotics were changed to intravenous meropenem. Atypical pneumonia cover with levofloxacin was discussed with the patient but due to the risk of potential teratogenicity, she declined this treatment.

She eventually had a CT thorax/abdomen/pelvis following discussion with the obstetric team to help establish possible infective sources or malignancy. Other than some mild inflammatory changes in the left lower lobe of her lung, there were no other remarkable features. A transthoracic echocardiogram did not show any evidence of cardiomyopathy or overt vegetation. An MRI spine and pelvis also did not show any evidence of discitis or a psoas abscess. Repeated microbiological investigations with blood cultures and extended viral screening including human immunodeficiency virus, Epstein-Barr virus, herpes simplex virus, influenza virus and cytomegalovirus were all negative. Autoimmune screen including antinuclear antibodies and anti-neutrophil cytoplasmic antibodies were negative as well.

She continued to have a persistent sinus tachycardia with sporadic episodes of pyrexia and rigors as well as worsening arthralgia, and many days elapsed before rheumatological opinion was sought. It was suspected that her clinical features were part of a systemic autoinflammatory process or cytokine hyperactivity, and the diagnosis became evident when the laboratory results were carefully reviewed and collated. Diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH) are listed in Table 2. Although her bone marrow examination did not demonstrate haemophagocytosis, this is not a necessary feature for the diagnosis and may only be observed late in the disease process. Genetic testing for primary HLH was unremarkable. As there was no microbiological or autoimmune cause found, this was therefore thought to be secondary HLH induced by pregnancy.

The HLH 2004 protocol[2] is normally aimed at treatment of patients with primary HLH prior to stem cell transplantation. It involves the use of chemotherapy which is potentially toxic during pregnancy. Potential delivery of the foetus and treatment with chemotherapy were discussed with her. However, as the foetus will likely be non-viable, it was agreed

with the patient that non-chemotherapeutic options be explored first and that delivery be postponed to a later date. Therefore, she was treated initially with a tapering dose of dexamethasone according to the HLH 2004 protocol[2] together with doses of pulsed intravenous methylprednisolone. The patient had a transient response where she became normothermic and her cardiovascular parameters normalised. However, her ferritin levels remained markedly elevated and a similar pattern of response was found with the use of intravenous immunoglobulin. She was eventually deemed fit to be discharged from the ICU to the haematology ward, as she no longer required respiratory or vasopressor support.

Following discussion with national experts, the MDT, the decision was taken to treat the patient with anakinra, an interleukin-1 (IL-1) receptor antagonist. It was felt that there was a need for additional treatment alongside high-dose corticosteroids. Although there has been clinical improvement, she remained intermittently pyrexial and her ferritin levels remained markedly elevated. Anakinra has shown substantial mortality benefit in a subgroup analysis of patients with HLH in a sepsis trial.[3] Furthermore, this drug has also been suggested to be safe for use in pregnant women.[4,5]

The patient had a significant positive response to the initiation of anakinra. She did not experience any further episodes of pyrexia, rashes or arthralgia. With subsequent dose adjustment, her ferritin levels decreased to around 2000 ng/mL two weeks into this treatment. The only side effect experienced was injection site reactions which were managed well with chlorphenamine. She was frequently reviewed by the obstetric team, while she was an inpatient and they had no foetal concerns. She was subsequently discharged at 27 weeks' gestation from hospital on a weaning course of anakinra and dexamethasone.

Her pregnancy progressed well with no significant problems and plans were made initially for induction at 38 weeks. At 31 + 5 weeks' gestation, however, there was evidence of intrauterine growth restriction on foetal wellbeing scan. Doppler of the umbilical artery showed an abnormally high pulsatility index with absence of end-diastolic flow, and subsequent cardiotocography was abnormal as well. She was therefore urgently admitted for a category 1 caesarean section. She delivered a baby boy who was monitored briefly in the neonatal unit. There were no foetal abnormalities identified, and both the patient and the baby boy were discharged from the hospital. Subsequent follow-up appointments over the next two months show that she remained well despite being weaned off anakinra, and ferritin levels remained low.

Discussion

HLH is a severe, rare, life-threatening haematological condition caused by an over activation of macrophages and lymphocytes which leads to uncontrolled proliferation and severe inflammation, as the T-lymphocytes, natural killer (NK) cells and macrophages release large amounts of cytokines. This leads to the clinical manifestations that are seen as in this case and the high risk of death without treatment. The first case report of HLH was published in 1952.[6] Since then, the understanding of HLH has grown exponentially.

Inheritance and pathophysiology

HLH is a disorder that can be inherited due to an underlying genetic defect known as primary or familial haemophagocytic lymphocytosis. This has an autosomal recessive inheritance causing mutations in the genes important for NK and T-cell cytotoxic function and thus causes an uncontrolled inflammatory response with activation of interferon gamma (IFNγ) producing T cells. High levels of IFNγ lead to macrophage activation and overproduction of pro-inflammatory cytokines and subsequently leads to severe tissue damage, cell death and organ failure.[7]

Secondary or acquired HLH is caused by over-activation of the immune system as a result of systemic infections (bacterial or viral), immunodeficiency or underlying malignancy.[8] Common malignancies associated with HLH include acute leukaemia and non-Hodgkin's lymphoma.[7] A retrospective study at the Mayo Clinic who had previously diagnosed 62 adults with secondary HLH found that 52% of them had underlying malignancy, 34% had a bacterial or viral infection, 8% had an autoimmune disorder and 6% had no obvious underlying cause.[9]

There are some published case reports of HLH in pregnancy which have been associated with various infective, autoimmune or malignancy-related causes.[10–15]

A diagnostic challenge

The diagnosis of HLH is often difficult as was shown in our case report. The symptoms, such as high fever, rash, pancytopenia, lymphadenopathy, hepatosplenomegaly and jaundice, can mimic an infection or initially appear non-specific In a pregnant patient, its presentation mimics that of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.[11] Neurological signs such as confusion, seizures and even coma can occur.[12,13] Due to the varying presenting features that can occur with HLH, there can be significant delays in diagnosis which increases mortality risk.

CRP and ferritin levels are usually markedly elevated. Hyperferritinaemia in adults is a non-specific diagnostic feature which can be elevated in many disease conditions but ferritin levels >10,000 ng/L in the paediatric population is highly sensitive and specific for HLH.[16] However, the rate of ferritin decline is of more of an interest in our case as ferritin level decline

has been suggested and used as a decent prognostic marker for patients with HLH. In our patient, she made a good clinical recovery which is mirrored by the declining trend of her serum ferritin levels.[17]

A bone marrow aspirate was done in our patient to look for evidence of haemophagocytosis. This feature is common in bone marrow aspirates of patients with HLH. However, the presence of haemophagocytosis does not reliably predict the probability of HLH.[18] In our patient, there was no evidence of haemophagocytosis on her bone marrow aspirate, but she still fulfilled the diagnostic criteria of HLH and was therefore treated as such.

Treatment options and dilemmas

The best treatment for HLH is still highly debated. The aims are mainly to treat the underlying trigger and to mitigate the overactive immune system. Treatment options in efforts to achieve the latter include high-dose corticosteroids, disease-modifying agents (e.g. cyclosporine, tacrolimus and intravenous immunoglobulin) and chemotherapy.[1] However, treatment with chemotherapy such as etoposide can cause bone marrow suppression and is not safe in pregnancy. As a result, the options for treatment in pregnancy are limited.[10,14]

Due to the high morbidity and mortality associated with this condition, it is worth considering delivery of the foetus prior to starting chemotherapy. However, the decision to deliver or terminate a pregnancy should always be discussed with the mother first, as they can come with a large physical and psychological burden to her. High-dose steroids are safe in pregnancy and are the first-line treatment of patients with HLH. This could sometimes be the only treatment needed to induce remission in pregnant patients as elucidated in several case reports.[14,15]

Our patient was later on treated with anakinra. This drug is normally used as a second-line treatment for patients with rheumatoid arthritis. It has been previously used in eight children with secondary HLH in 2011–2012 with promising results.[19] There have been limited data on the use of anakinra in the pregnant population and it is unknown whether they can bring harm to the unborn foetus. They have been, however, used before in pregnant patients to treat other conditions.[4,5]

Prognosis

Prognosis for patients with HLH is guarded, especially if poor prognostic factors such as malignancy are present. Studies showed that 50% of HLH patients with underlying malignancy died by 1.4 months compared to 22.8 months without underlying malignancy.[9] Primary HLH is nearly fatal without treatment. However, chemotherapy treatment and stem cell transplant have revolutionised its management and can result in a cure. Secondary HLH mortality in adults is high, but limited by small data. A case series of adults treated with a variety of regimens report a 30-day mortality of 20–44% and an overall mortality of 50–75%.[20,21]

Learning points

- HLH is an aggressive and life-threatening syndrome of excessive immune activation. It is most common in infants and young children, but can affect patients of any age, with or without a predisposing familial condition.
- HLH is rare and its diagnosis during pregnancy can be challenging. Pregnancy in this case was thought to trigger immune dysregulation which can culminate in the clinical features of HLH. Other secondary triggers include infection, malignancy and rheumatologic disorders, e.g. juvenile idiopathic arthritis.
- The diagnosis of HLH is made by identifying a mutation in an HLH gene, or by fulfilling five of eight diagnostic criteria. Haemophagocytosis, while often seen in histological samples, is neither necessary nor sufficient for the diagnosis of HLH.
- A pronounced hyperferritinaemia in the setting of systemic features of an inflammatory response with negative infectious and rheumatological workup should raise the suspicion of HLH.
- Untreated patients with HLH have a mean survival of months, due to progressive multi-organ failure. Survival can be dramatically increased with HLH-specific therapy. Therapy should be based on clinical suspicion and should not be delayed while awaiting specialized immunologic testing or genetic analysis.

Informed consent

We declare that we have obtained a signed written consent from the patient for this case report.

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