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Neonatal Haemophagocytic Lymphohistiocytosis Associated with Maternal Adult-Onset Still's Disease

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Established Facts

- Haemophagocytic lymphohistiocytosis (HLH) is a very rare and life-threatening disease which is usually of familial origin.

Novel Insights

- This is the first reported case of HLH associated with maternal Still's disease.
- In infants having a systemic inflammatory response associated with active maternal rheumatological or autoimmune diseases, neonatologists should consider HLH as prompt treatment with corticosteroids and/or chemotherapy could be life saving.

Key Words
Cytopenia · Haemophagocytic lymphohistiocytosis · Infants · Still's disease

Abstract
Neonatal haemophagocytic lymphohistiocytosis (HLH) is a rare but potentially lethal condition. We recently encountered a preterm infant who developed severe HLH associated with maternal adult-onset Still's disease, which to our knowledge has not been previously reported. The infant presented with fever, generalised lymphadenopathy, transient erythematous skin rash, hepatosplenomegaly, ascites, pancytopenia, marked hyperferritinaemia, and hypofibrinogenaemia, which were features similar to maternal presentation during late pregnancy. Whole gene exome sequencing screening for familial HLH (*PRF1*, *STX11*, *STXBP2*, and *MUNC13D* genes) was negative. We postulated that factors such as auto-antibodies, antigens, or inflammatory mediators transmitted vertically from the mother could have triggered the intense inflammation in the infant. The infant responded promptly to dexamethasone, etoposide, and cyclosporin A, without the need for bone marrow transplantation. Neonatologists should be alerted to the rare diagnosis of HLH in the presence of active maternal diseases, including infection or autoimmune conditions, especially in association with fever, cytopenia, and hepatosplenomegaly.

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a rare condition secondary to the unrestrained proliferation of activated lymphocytes or histiocytes and an ineffective immunological response resulting in the abundant release of inflammatory cytokines and chemokines. It has been conventionally classified into primary familial HLH and secondary acquired disease [1–4]. Oftentimes, neonatal presentation is due to familial disease [1] or pathogen-associated secondary cases [2, 3]. We recently encountered a case of acquired HLH in a preterm infant associated with maternal adult-onset Still's disease, which to the best of our knowledge has not been reported previously. It is important for frontline neonatologists to recognise its unusual presentation in the early postnatal period, as this condition carries a high mortality if not appropriately managed. Written consent was obtained from the patient's mother for this report.

Case Report

A female infant was born at 35 weeks' gestation with a birth weight of 2,445 g to a mother with active adult-onset Still's disease diagnosed at 32 weeks of pregnancy. The mother's signs and symptoms included high-spiking and persistent fever, erythematous rash, arthralgia, generalised lymphadenopathy, hepatosplenomegaly, and an elevated erythrocyte sedimentation rate of 76 mm/h. Extensive work-up was performed and the mother was confirmed to have adult-onset Still's disease according to Yamaguchi criteria. She had a raised titre of circulating anti-nuclear antibodies, but other auto-antibody markers were negative. The mother was subsequently treated with systemic corticosteroids with rapid regression of clinical features. The parents were non-consanguineous.

The infant was seemingly normal apart from mild prematurity at birth. On day 7, she was incidentally found to have hepatosplenomegaly (2 cm), generalised lymphadenopathy, and thrombocytopenia (87×10^9/l). A blanchable, erythematous, maculopapular rash transiently appeared on the trunk but subsided spontaneously within 48 h. Serum C-reactive protein was markedly elevated to 132 mg/l. Thus, a full sepsis screening, including blood, urine, and cerebrospinal fluid (CSF) cultures was performed. On day 15, despite being covered with broad-spectrum antibiotics, the patient continued to deteriorate with the recurrence of a maculopapular rash, increasing hepatosplenomegaly (4–5 cm) with deranged liver function (alanine transaminase 237 IU/l) and elevated lactate dehydrogenase (3,262 U/l), high fever (39°C), severe hypotension requiring multiple inotropes, including dopamine, dobutamine, and adrenaline, and respiratory failure necessitating high-frequency oscillatory ventilation and high oxygen concentration supplementation (FiO_2 80%). Repeat haematological evaluation revealed pancytopenia (haemoglobin 8.1 g/dl, neutrophil counts 0.2×10^9/l, and platelet counts 5×10^9/l) and deranged clotting profiles (prothrombin time 28 s and partial thromboplastin time 65.1 s) which required multiple packed cells, platelets, and fresh-frozen plasma transfusions. She was also found to have marked hyperferritinaemia (175,824 pmol/l, reference range 29–333 pmol/l) and hypofibrinogenaemia (0.71 g/l, reference range 2.03–4.09 g/l). Abdominal ultrasound confirmed ascites. Importantly, skin biopsy showed features of lichenoid dermatitis and nodular keratinocytosis suggestive of adult-onset Still's disease. Other investigation results were (i) CSF, blood, urine, and surface swab cultures did not grow any pathogens; (ii) viral screening for toxoplasma (IgG antibody), Epstein Barr virus (IgM antibody to viral capsid antigen), rubella (IgM antibody), cytomegalovirus (urine shell vial culture and PCR detection for cytomegalovirus DNA), enterovirus (RT-PCR RNA), herpes simplex virus (CSF, PCR DNA), and parvovirus (IgM antibody) were all negative, and ophthalmological assessment did not reveal features indicative of congenital infection; (iii) paired blood and urine metabolic screening yielded normal metabolite patterns; (iv) auto-antibody screening, including anti-nuclear antibodies, anti-dsDNA, anti-neutrophil cytoplasmic, anti-cardiolipin antibodies, and anti-extractable nuclear antigens (Sm, RNP, La, Ro, Jo-1 and Scl-70) were negative; (v) immunological screening showed normal CD4/CD8 cell ratio, though serum immunoglobulins IgA, IgG, and IgM were marginally decreased (0.07, 2.18, and 0.17 g/l, respectively), and (vi) screening via whole exome sequencing analysis for familial HLH genes *(PRFI, STX11, STXBP2*, and *UNC13D)* and primary immunodeficiency syndromes such as Chédiak-Higashi syndrome, Griscelli syndrome, and X-linked lymphoproliferative diseases (mean depth of target regions was 51.6× with 98% of target regions covered by more than 1× read depth) were also negative. Although bone marrow aspiration was performed on two occasions, both specimens were quantitatively insufficient for assessment.

The infant was treated as HLH with dexamethasone (10 mg/m^2/day) commencing on day 20. The fever and rash resolved within 72 h, and there was a gradual decrease in hepatosplenomegaly (2–3 cm) in the following week. Pancytopenia, hyperferritinaemia, and hypofibrinogenaemia also improved. Upon weaning of systemic dexamethasone (5 mg/m^2/day) on day 41, her clinical symptoms recurred and laboratory parameters worsened; thus, she was subsequently started on etoposide (150 mg/m^2/dose, weekly) and cyclosporin A (1.5 mg/kg/dose, every 12 h with weekly adjustment) on day 56 for a total of 9 weeks. Granulocyte colony stimulating factor (5 μg/kg/day, if neutrophil count $<0.5 \times 10^9$/l) was also added to the regime for the treatment of severe neutropaenia. The child is currently 11 months of age, and dexamethasone was stepwisely weaned off after the completion of chemotherapy. While on a maintenance dose of cyclosporin A, serum ferritin and fibrinogen levels normalised, and she has had continued disease regression with no further disease relapses.

Discussion

The infant fulfilled the diagnostic criteria of HLH according to the HLH-2004 treatment protocol [5] by presenting with 5 of 8 clinical features, including high fever, hepatosplenomegaly, cytopenia, marked hyperferritinaemia, and hypofibrinogenaemia. Typically, HLH infants present with clinical features mimicking severe sepsis or

pneumonia with high circulating levels of acute phase reactants and/or pulmonary infiltrates. However, in contrast to septic patients, they have negative microbial cultures and are unresponsive to anti-microbial agents, and continue to run a rapidly downhill course unless appropriate therapy is instituted. Importantly, it is likely that our patient acquired secondary HLH via vertical transmission of factors from her mother, who had active adult-onset Still's disease during pregnancy. This is evidenced by (i) the close similarities in clinical features shared by both mother and infant, such as fever unresponsive to antibiotics, hepatosplenomegaly, ascites, generalised lymphadenopathy, transient erythematous skin rash, and persistently high acute-phase proteins before corticosteroid therapy; (ii) the absence of known gene mutations for familial HLH, and (iii) prompt response to systemic corticosteroids and chemotherapy without the recurrence of disease or the need for bone marrow transplantation, which suggests the infant's condition is not permanent.

Secondary HLH is usually associated with infection [2, 3], malignancy, and autoimmune or rheumatological conditions [4]. Although the exact mechanism in our patient cannot be fully elucidated, it is plausible that immunological factors such as auto-antibodies, antigens, or inflammatory mediators transferred vertically from the mother may have triggered similar immunological responses in the infant. The temporal relationship of disease onset and the self-limiting nature of the inflammation suggest that such transient factors induced an exaggerated pro-inflammatory reaction similar to the case described in maternal Sjogren syndrome [4]. The latter case also had an intense inflammatory response which was controlled by systemic hydrocortisone and without the need for transplantation. Of all aetiologies associated with secondary HLH cases, autoimmune-related HLH is probably the least reported in correlation with early-onset neonatal diseases. As far as we are aware, this is the first reported case of adult-onset Still's disease associated neonatal HLH.

It is of paramount importance that frontline neonatologists are able to recognise this rare but potentially life-threatening condition and must not confuse HLH with the more common neonatal sepsis. The presence of clinical history with parental consanguinity with or without previous sibling loss, or active maternal diseases such as infection or autoimmune rheumatological conditions in association with the three most common features of fever, cytopenia (2 out of 3 lineages), and hepatosplenomegaly in an infant unresponsive to anti-microbial agents should alert neonatologists to the possibility of HLH [5]. The prompt institution of isolation precaution and treatment with corticosteroids and chemotherapy are life saving for this otherwise lethal condition.

Disclosure Statement

No funding was received for this study. The authors declare no conflicts of interest.

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