CASE REPORT

Forme Fruste of HLH (haemophagocytic lymphohistiocytosis): diagnostic and therapeutic challenges

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SUMMARY

Infants and young children often present with a persistent febrile episode, sick appearance and negative infectious disease work-up. These patients present serious diagnostic and therapeutic problems to those who provide medical care, particularly since these children are clinically sick. We present a 13 month old child who presented with this clinical challenge. She was ultimately thought to have an incomplete form of HLH with underlying pathophysiology of hypercytokinemia, but also could have been a case of incomplete form of Kawasaki disease. She responded to IVIG, but this does not differentiate one diagnosis from another. Unfortunately we failed to obtain tests to exclude genetic etiologies of HLH, which would be important for predicting severity and risks of future recurrence. We wish to present this case so that one should do a thorough work up to establish a firm diagnosis of HLH and to search for genetic causes of this disorder.

BACKGROUND

Young children with persistent high fever without evidence of bacterial, fungal or viral infection who do not respond to systemic antibiotics present diagnostic as well as management problems, yet these cases are not very rare. We present a case of a young child with persistent fever, with no evidence of infection, who exhibited clinical and laboratory characteristics of haemophagocytic lymphohistiocytosis (HLH) as well as some features of Kawasaki disease. We wish to underline the similar pathogenic mechanisms of these two syndromes (HLH and Kawasaki disease) using this case as well as citing published cases in the literature. We suggest that it would be important to carry out a thorough work up for firm evidence of HLH including genetic causes. It would be advisable to institute appropriate therapy even in cases that may not meet all the diagnostic criteria of HLH or Kawasaki disease.

CASE PRESENTATION

A 13-month-old, previously healthy female baby developed high fever (up to 40° C) and irritability without any other symptoms such as cough, ear pain, rash, oral lesions, conjunctival injections, lymph node enlargement, vomiting or diarrhoea. She was hospitalised on day 3 of fever. At that time her temperature was 40.5°C, and she was irritable and inconsolable. Except for mild nasal congestion and perineal erythema, the physical examination was normal. Pertinent laboratory results and the maximum temperature each day of the hospital course are shown in table 1 below.

During her hospital stay, the patient continued to be febrile. Fever lasted for a total of 9 days in spite of systemic antibiotics. She received intravenous immunoglobulins (IVIG; 1 g/kg/day) on days 4 and 5 of hospital stay. Subsequently, she received 90 mg/kg/day of aspirin daily for the first 14 days, and a lower dose for the subsequent 6 weeks. She defeveresced on seventh hospital day following the second IVIG dose. She did not show enlarged lymph nodes, liver or spleen, and had no systemic rash other than perineal erythema. There was no redness or indurations of hands or feet, desquamation of the skin, or conjunctival injections throughout the hospital course. An echocardiogram performed on day 2 of hospital stay as well as an echocardiogram performed 6 weeks later showed no coronary dilation or aneurysm. The patient eventually uneventfully recovered from this febrile illness. She is doing well now 6 months after the initial febrile episode.

INVESTIGATIONS

Laboratory results were: serum lactate dehydrogenase (LDH) 379U/L (100–295), ferritin 1299 ng/mL (10–291) and triglyceride 164 mg/dL (1.85 mmol; 30–154 mg/dL; 0.34–1.75 mmol). Prothrombin time 12.7 s (12.0–14.7), activated partial thromboplastin time 36 s (23.3–35.7) and fibrinogen 443 mg/dL. Serial aspartate transaminase (AST) and alanine transaminase (ALT) remained normal; the patient did not have hyponatremia at any time. Additional tests for infectious diseases were carried out as follows, and they were either all negative, no growth, non-reactive or not detected. Adenovirus by PCR, rhinovirus by PCR, influenza A and B by rapid tests, enterovirus in cerebrospinal fluid (CSF) by PCR, parvovirus B19 IgG and IgM, and parvovirus DNA by PCR, cytomegalovirus IgG and IgM, Epstein-Barr virus (EBV) IgG and IgM, histoplasma and legionella antigens in urine, listeria monocytogenes complement fixation antibodies, rapid plasma reagin in blood, Venereal Disease Research Laboratory in CSF, blood, urine and CSF cultures. CSF showed no pleocytosis and normal protein and glucose. Stools were tested for *Salmonella*, *Shigella*, *Campylobacter*, *Giardia* and *Cryptosporidium* toxins, rotavirus antigen, *Clostridium difficile*, and Shiga-like toxins antigens I and II. They were all negative or no growth.

On the third hospital day, bone marrow aspiration and biopsy showed mildly hypocellular

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Table 1 Serial CBC and body temperature

Hospital day	1	2	3	4	5	6	8	11*	19	50
Haemoglobin	11.3	10.3	10.8	11	9.5	9.5	9.4	8.7	11	12.5
WCC	7.1	4.9	4.1	4.9	4.7	9.3	7.4	16.0	8.2	7.2
ANC	4.1	3.0			1.9		1.9			
Platelets	87	71	60	119	138	177	334	770	502	256
CRP	10.643	9.355	8.060	3.996			0.657	0.027	<0.016	
ESR					107		>120	44	16	
Highest temperature		40.5	40.0	39.5	39.7	39.2	39.2	36.5		

*Day of discharge.
ANC, absolute neutrophil count; CBC, complete blood count; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; WCC, white cell count.

marrow with trilineage elements. There were histiocytes and phagocytes, with nucleated red cells and neutrophils, within the cytoplasm, indicating phagocytosis. Absolute reticulocyte count was only 0.01 (10 000)/μL, indicating decreased erythropoiesis.

Natural killer (NK) cell function was normal, but soluble interleukin 2 receptors (IL-2R) were 3172 μ/mL (406–1100). Rheumatoid factor and antinuclear antibody were negative, and serum IgG, IgA and IgM were normal. IgD was not measured.

DIFFERENTIAL DIAGNOSIS

The patient presented with a sick appearance and high fever that were only temporarily partially responsive to antipyretics. The differential diagnoses in this case were broad, and included infectious diseases, malignancy and autoimmune diseases. However, in spite of the exhaustive search for infectious agents, none was found, making infection an unlikely cause of fever. Systemic onset of idiopathic juvenile arthritis was also a possibility, but the patient never developed typical rash or hepatosplenomegaly. Other autoimmune diseases considered were inflammatory bowel disease, polyarteritis nodosa and antineutrophil cytoplasmic antibody associated vasculitis,[1] or a very rare hereditary disorder, mevalonic acid kinase deficiency[2] or other periodic fever syndrome, though the latter cannot be suspected unless febrile episodes are repeatedly observed. Our patient, however, showed no signs or symptoms suggestive of any of these disorders. A form of systemic vasculitis, Kawasaki disease, was seriously considered[3] in spite of absence of characteristic physical signs except for fever, and perhaps perineal erythema. The criteria for the diagnosis of Kawasaki disease are: fever of at least 5 days' duration and at least four of the five following features: changes in the extremities, polymorphorous exanthema, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical lymphadenopathy, and exclusion of other diseases with similar findings.[3]

Even though erythrocyte sedimentation rate (ESR), C reactive protein (CRP) and fibrinogen in our patient were highly elevated, these are non-specific inflammatory markers. Anaemia and subsequent thrombocytosis were also consistent with Kawasaki disease, but they are non-specific. Nonetheless, infants and small children are known to present with atypical clinical findings. And thus we were unable to entirely exclude Kawasaki disease. Since early treatment with IVIG is essential to prevent coronary artery lesions, we gave IVIG to our patient.

The persistent fever as well as multiple laboratory values in this patient fit a diagnosis of HLH. The most recent diagnostic criteria for acquired HLH are meeting at least five of the following eight criteria: fever, splenomegaly, cytopenias (two of the three, haemoglobin (Hb) <9 g/dL, platelet <100 000/μL, absolute neutrophil count (ANC) <1000/μL), hypertriglycidemia (≥3 mmol/L) and/or hypofibrinogenemia (<150 mg/dL), serum ferritin above 500 μg/L, soluble IL-2R (sIL-2R) ≥2400 U/mL, decreased or absent NK cell activity and haemophagocytosis in the bone marrow, CSF or in the lymph nodes.[4] Of these, our patient had fever, thrombocytopenia and anaemia (only on 1 day), high serum ferritin, elevated IL-2R and marrow phagocytosis. Thus our patient marginally met four of the eight criteria. However, the NK cell activity was not low or absent (the hallmark of hereditary HLH), and fibrinogen was elevated rather than decreased. Furthermore, a combination of persistently normal liver enzymes and blood sodium, and markedly elevated ESR, normal ANC and absence of splenomegaly tended to mitigate against this diagnosis. In spite of these inconsistent laboratory values, the clinical features together with most of the laboratory findings were consistent with the diagnosis of HLH. Since we did not perform genetic testing for HLH, we were unable to determine if our patient had a hereditary form or acquired form. Hereditary or familial forms of HLH (FHLH) are now subclassified into five subtypes based on each genetic abnormality. FHLH 2, 3, 4 and 5 are due to mutations in genes encoding perforin (*PRF-1*), genes encoding Munc-13–4 (UNC13D), syntaxin 11 (STX11) and syntaxin-binding protein 2 (STXBP2), respectively.[5] Genes responsible for FHLH type 1 have not been identified. Although other hereditary autosomal recessive disorders such as Griscelli syndrome type II, Hermansky-Pudlak syndrome, or Chediak-Higashi syndrome, do frequently present with HLH, these syndromes accompany distinguished physical features such as albinism, and therefore any of these syndromes could be ruled out. Thus, although ultimately we were unable to exclude a hereditary form of HLH, we believe that it is unlikely because of the normal NK cell activity in our patient. It is noteworthy that this patient responded to IVIG treatment, which was originally prescribed for Kawasaki disease. 'Mild cases' of HLH have been shown to respond to IVIG.[6–9]

TREATMENT

IVIG, 1 g/kg of body weight/day, daily×2 days.

Aspirin 90 mg/kg/day daily for the first 2 weeks, then at a lower dose daily for the subsequent 6 weeks.

OUTCOME AND FOLLOW-UP

The patient recovered completely and had no cardiac abnormalities 6 months following discharge.

DISCUSSION

Our patient demonstrated some typical laboratory values highly suggestive of HLH, yet she marginally met the diagnostic criteria and, furthermore, there were other laboratory values that were inconsistent with this diagnosis. We treated the patient

with IVIG 'prophylactically' with a working diagnosis of possible Kawasaki disease, even though she failed to meet diagnostic criteria, and, ultimately, she did not show any coronary artery abnormalities. Nonetheless, it appears that the patient seemed to have responded to the two doses of IVIG infusions.

Imashuku[8] proposed a clinical staging of EBV-associated HLH severity into mild, intermediate and severe depending on clinical, laboratory and genetic factors. He suggested a therapeutic strategy: "the patients may be stratified into (a) those needing immediate treatment with HLH-94/2004 and (b) those for whom a 'watch and wait' policy can be adopted or who can be treated conservatively with corticosteroids or IVIG or CsA." According to his staging criteria, our patient, though not EBV associated, had mostly mild features such as lack of coagulopathy, capillary leak syndrome, jaundice or neurological symptoms, and values of most laboratory values (AST, ALT, sIL-2R, LDH and ferritin) together with some laboratory features of intermediate staging, such as a platelet count of 50 000–100 000 and Hb between 7 and 9 g/dL. The author[8] asserted that presence of a genetic factor put patients in the severe, high-risk group. However, hereditary factor investigations are usually time consuming and not immediately available for risk-based treatment options.

A literature review demonstrated multiple cases of Kawasaki disease followed by development of HLH.[10–18] In these patients, fever was usually biphasic, initially responding to the IVIG treatment only to recur later, or refractory to IVIG with subsequent development of cytopenia, coagulopathy, hepatosplenomegaly and worsening of clinical conditions. Although there is an overlapping pattern of hypercytokinemia, such as an elevation of IL-6 and tumour necrosis factor (TNF) in HLH as well as in Kawasaki disease, interferon-γ and IL-1β are distinct, the former elevated during HLH phase but not during Kawasaki phase, whereas the opposite is true for IL-1β. Ohga *et al* emphasised the importance of the ratio, interferon-γ/TNF as the distinguishing feature of the two syndromes, the higher level indicating HLH.[7]

A case published by Titze *et al*[12] is quite illustrative in this regard: A 7-week-old infant developed persistent high fever. Originally the patient had leukocytosis and bandemia, normal liver enzymes and fibrinogen levels, and a highly elevated CRP. In addition, the infant had a rash and conjunctivitis. Laboratory values showed markedly decreased NK cell function, increased sIL-2R and markedly increased TNF-α. These findings are more consistent with Kawasaki disease than HLH, however, later the platelet count fell and abdominal ultrasound showed 'marked hepatosplenomegaly'. At this point, the patient met the criteria for HLH and was treated with dexamethasone, cyclosporine and etoposide per HLH-2004 protocol.[5] The patient clinically promptly responded, but died 28 days later of myocardial infarction confirmed by autopsy; however, the infant did not have coronary artery aneurysm. The authors interpreted this case to show that the patient died of a coronary artery complication of Kawasaki disease. This patient was not treated by IVIG, since the patient was initially not suspected to have Kawasaki disease. This case may be reclassified as an atypical case of Kawasaki disease. The sequence of events described in this case report is very typical of other published cases that started with Kawasaki disease and later developed HLH, except that most cases had been treated with IVIG during the Kawasaki disease phase.

We speculate that the underlying pathophysiology in our patient is very similar to that of HLH and most likely it represents inappropriate upregulation of cytokines perhaps triggered by an unidentified infectious agent. In that regard, one may regard this as Forme Fruste of HLH, since the case does not meet all the diagnostic criteria. However, it may be reasonable to manage this type of case as if the patient had HLH. Our patient may have had an incomplete form of KD, though the patient lacks needed physical findings to make a diagnosis of KD. Whether the patient developed coronary aneurysm without IVIG and aspirin will remain unanswered.

Some cases in older reports, describing thrombocytopenia together with hypofibrinogenemia, reduced ESR and elevated CRP, may have had HLH; such as the one described by Titze *et al*.[12] Another example may be case 10 of Niwa *et al*'s[19] reported series. This patient had late onset thrombocytopenia, hypofibrinogenemia and myocardial infarction. The patient described by Crowchuk *et al*[20] had thrombocytopenia as well as neutropenia (with normal white cell count) and anaemia.

We consider both Kawasaki disease and HLH as inappropriate hypercytokinemia (cytokine storm) triggered by a variety of factors such as infection, malignancy, etc, and greatly modified by genetic heterogeneity in response to infection or inflammation. In the original description of cytokine storm that was triggered by a phase I monoclonal antibody, anti-CD28 (TGN1412), TNF-α, interferon-γ, and IL-2, IL-4, IL-6, IL-8 and IL-10, markedly increased during the immediate postinfusion period. At the same time there was a marked decrease in Hb, platelet count, lymphocytes and monocytes.[21] These changes are markedly similar to the characteristics of HLH, except that there was no neutropenia. We believe that patterns of cytokine and haematological abnormalities may vary depending on the individual's genetic predispositions, types of triggering events and type of cytokines most prominently produced. Thus one should not rigidly adhere to strict diagnostic criteria to initiate measures to mitigate cytokine storm effects. In this regard, authors who managed the patients who had received TGN1412 successfully used anti-IL-2R and high-dose steroids to treat the storm. We believe that a case such as ours, although failed to meet diagnostic criteria in a strict sense, should be managed in the same way hyper inflammatory conditions are managed, with IVIG, high-dose steroids and other accepted therapy for HLH,[5] starting with least invasive treatment, escalating to more invasive and intensive treatment depending on the patient's response. In this regard, we completely agree with the treatment strategy described by Imashuku.[8] Although his strategy is focused on only EBV-associated HLH, we believe that it can be generalised to HLH triggered by other agents. Rajasekaran *et al*[22] reported successful treatment of eight paediatric intensive care unit patients with presumed secondary HLH with IL-1R antagonist (anakinra). Thus treatment of HLH could be directed to those particular cytokines that are causing organ damage in addition to, or in place of non-specific immunosuppressants.

Conclusions

We presented a sick febrile child who had several features of HLH, but not entirely fulfilling the diagnostic criteria. However, we regard this as an incomplete form of HLH, or mild clinical stage of HLH. One should manage these patients in a way similar to the management of HLH. However, the intensity of management should reflect the severity of illness, or clinical staging. In our case, administration of IVIG two doses was adequate to resolve this illness. It would be important to do a thorough genetic work up for HLH during the acute phase, since genetic predisposition puts patients in a high-risk/high-mortality group.

Learning points

- An infant or a toddler presenting with persistently high fever presents diagnostic and therapeutic challenges.
- There are incomplete forms, or mild clinical stages of HLH with identical pathophysiology but not as severe as a full blown, or severe stage of HLH.
- Identifying underlying cytokine pattern and investigation of genetic factors are important in deciding on appropriate management and prognostication, if clinical and laboratory pictures do not fulfil diagnostic HLH criteria.

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REFERENCES

1 Smith RM, Jones RB, Jane DW. Progress in treatment of ANCA associated vasculitis. *Arthritis Res Ther* 2012;14:210.
2 Thors VS, Vastert SJ, Wulffraat N, *et al*. Periodic fever in MVK deficiency: a patient initially diagnosed with incomplete Kawasaki disease. *Pediatr* 2014;133:e461–5.
3 Dajani AS, Taubert KA, Gerber MA, *et al*. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776–80.
4 Janka GE, Lehmberg K. Hemophagocytic lymphohistiocytosis: pathogenesis and treatment. *Hematology Am Soc Hematol Educ Program* 2013;2013:605–11.
5 Chandrakasan S, Filipovich AH. Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. *J Pediatr* 2013;163:1253–9.
6 Lin CI, Yu HH, Lee JH, *et al*. Clinical analysis of macrophage activation syndrome in paediatric patients with autoimmune disease. *Clin Rheumatol* 2012;31:1223–30.
7 Alvarez-Cardona A, Rodriguez-Lozano AL, Blancas-Galicia L, *et al*. Intravenous immunoglobulin treatment for macrophage activation syndrome complicating chronic granulomatous disease. *J Clin Immunol* 2012;32:207–11.
8 Imashuku S. Treatment of Epstein-Barr virus-related hemophagocytic lymphohistiocytosis (EBV-HLH); update 201. *J Pediatr Hematol Oncol* 2011;33:35–9.
9 Hot A, Madoux MH, Viard JP, *et al*. Successful treatment of cytomegalovirus-associated hemophagocytic syndrome by intravenous immunoglobulins. *Am J Hematol* 2008;3:159–62.
10 Muise A, Tallett SE, Silverman ED. Are children with Kawasaki disease and prolonged fever at risk for macrophage activation syndrome? *Pediatr* 2003;112:e495–7.
11 Ohga S, Oohshima A Fukushige J, *et al* Histiocytic haemophagocytosis in a patient with Kawasaki disease: changes in the hypercytokinaemic state. *Eur J Pediatr* 1995;154:539–41.
12 Titze U, Janka G, Schneider EM, *et al*. Hemophagocytic lymphohistiocytosis and Kawasaki disease: combined manifestation and differential diagnosis. *Pediatr Blood Cancer* 2009;53:493–5.
13 Kang H-R, Yong-hoon Kwon Y-H, Eun-Sun Yoo E-S, *et al*. Clinical characteristics of hemophagocytic lymphohistiocytosis following Kawasaki disease: differentiation from recurrent Kawasaki disease. *Blood Res* 2013;48:254–7.
14 Chen Y, Shang S, Zhang C, *et al*. Hemophagocytic lymphohistiocytosis at initiation of Kawasaki disease and their differential diagnosis. *Pediatr Heamtol Oncol* 2010;27:244–9.
15 Kim HK, Kim HG, Cho SJ, *et al*. Clinical characteristics of hemophagocytic lymphohistiocytosis related to Kawasaki disease. *Pediatr Hematol Oncol* 2011;28:230–6.
16 Palazzi DL, McClain KL, Kaplan SL. Hemophagocytic syndrome after Kawasaki disease. *Pediatr Infect Dis J* 2003;22:663–5.
17 Hendricks M, Pillay S, Davidson S. *et al* Kawasaki disease preceding hemophagocytic lymphohistiocytosis: challenges for developing world practioners. *Pediatr Blood Cancer* 2010;54:1023–5.
18 Simonini G, Paganini I, Innocenti L. Macrophage activation syndrome/hemophagocytic lymphohistiocytosis and Kawasaki disease. *Pediatr Blood Cancer* 2010;55:591.
19 Niwa K, Aotsuka H, Hamada H, *et al*. Thrombocytopenia: a risk factor for acute myocardial infarction during the acute phase of Kawasaki disease. *Coronary Artery Dis* 1995;6:857–64.
20 Crowchuk DP, Kumar M, Vielhaber MM, *et al*. Kawasaki disease presenting with thrombocytopenia. *Am J Dis Child* 1990;144:19–20.
21 Suntharalingam G, Perry MR, Ward S, *et al*. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. *N Engl J Med* 2006;355:1018–28.
22 Rajasekaran S, Kruse K, Kovey K, *et al*. Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. *Pediatr Crit Care Med* 2014;15:401–8.