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Severe Lactic Acidosis in an Infant with Haemophagocytic Lymphohistiocytosis

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Abstract Haemophagocytic lymphohistiocytosis (HLH) is a rare disease with high mortality. We report a one-month-old infant presented with fever, pancytopenia, liver derangement, coagulopathy, and was subsequently diagnosed to have HLH. No secondary cause could be identified after extensive workup. She developed multi-organ failure with severe lactic acidosis that was refractory to other treatment. Continuous renal replacement therapy successfully corrected her lactic acidosis. Our case highlights the importance of monitoring serum lactate level in critically ill patients with severe metabolic acidosis.

Key words Continuous renal replacement therapy; Haemophagocytic lymphohistiocytosis; Lactic acidosis

History

A previously healthy 34-day-old infant girl born at full term by normal vaginal delivery was admitted for fever with no localising symptoms. She had unremarkable perinatal and family history. Examination revealed a febrile infant with rectal temperature of 39.7ºC. Her blood pressure was 71/54 mmHg, her pulse rate was 166 beats per minute and respiratory rate was 48/minute. Skin mottling was noted and the capillary refill was two seconds. Other examinations were unremarkable.

Her blood count showed thrombocytopenia with platelet count 91×10^9/L (Normal: 143-380$\times10^9$/L), haemoglobin 11.1 g/dL, and the white blood cell was 5.6×10^9/L with neutrophils 1.5×10^9/L and lymphocytes 3.1×10^9/L. The alanine transaminase (ALT) was 69 IU/L (Normal: 3-30 IU/L), and other parameters of liver function test were within normal range. C-reactive protein was 23.4 mg/L (Normal: <5 mg/L). The chest X-ray did not show any abnormality. She was started on ampicillin and gentamicin empirically after sepsis workup. Her fever persisted and examination revealed progressive hepatosplenomegaly with the liver palpable at five centimeters below the right costal margin and the spleen palpable at one centimeter below the left costal margin. Despite negative culture, her antibiotic was changed to vancomycin and meropenem.

Subsequent blood tests showed worsening of pancytopenia, deranged liver function and lactic acidosis (Table 1). The prothrombin time (PT) and activated partial thromboplastin time (APTT) were 32 seconds (Normal: 13–16 seconds) and 90 seconds (Normal: 30–36 seconds) respectively and the international normalised ratio (INR) was 3.36 (normal range 0.9–1.3). Decreased fibrinogen 0.54 g/L (Normal: 1.5–4.0 g/L) and elevated D-dimer 3805 ng/ml fibrinogen equivalent unit (FEU) (Normal: <500 ng/ml FEU) were also detected.

Her β-hydroxybutyrate level was 0.09 mmol/L (Normal: <0.27 mmol/L), and there was no hypoglycaemia. Extensive metabolic workup was therefore performed and she was started on cocktail vitamins, carnitine supplement and coenzyme Q10 supplement for possible inborn error of metabolism. Both the free and total carnitine level and

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acycarnitine pattern were normal. Spot urinalysis was negative for ketone. Urine reducing substance was negative. Urine amino acid analysis showed generalised aminoaciduria with relative prominence of phenylalanine and alanine. Plasma amino acid analysis also repeatedly showed increased tyrosine, phenylalanine and alanine, which can be explained by concomitant liver failure, histiocytosis and high lactate level. Urine organic acid showed increased lactic acid, branched chain keto-acids and other non-specific organic acids. Urine 2,4-dinitrophenylhydrazine (DNPH) test for possible maple syrup urine disease was negative. Clinical Genetic Service was consulted for possible mitochondriopathy due to the severe lactic acidosis, and DNA analysis did not detect mitochondrial mutation accounting for approximately 90% of MELAS (Mitochondrial Encephalopathy, Lactic Acidosis and Stroke-like episodes) and MERRF (Myoclonic Epilepsy and Ragged Red Fiber) phenotype, 10-20% of Leigh syndrome and 50% of NARP (Neuropathy, Ataxia and Retinitis Pigmentosa) phenotype.

Bone marrow aspiration performed three days after admission showed increased histiocytes forming aggregates focally and a small percentage showed haemophagocytic activities, the erythroid precursors were normoblastic and active megakaryocytopoiesis was observed, and there was no increase in blast component. Bone marrow karyotype was 46,XX. The serum ferritin level was highly elevated at 18513 pmol/L (Normal: 81–739 pmol/L) but the triglyceride level (0.6 mmol/L) was not increased. The diagnosis of haemophagocytic lymphohistiocytosis was therefore made four days after admission based on (1) fever; (2) splenomegaly; (3) pancytopenia; (4) hypofibrinogenaemia; (5) high ferritin level and (6) haemophagocytosis in bone marrow.

Immunotherapy was started according to the Treatment Protocol of the Second International HLH Study 2004 (HLH-2004). Dexamethasone and cyclosporin A were started two days after bone marrow examination, and etoposide was commenced one day later.

However, her renal function and the lactic acidosis worsened. Her total bilirubin level rose to 214 μmol/L (Normal: 5–27 μmol/L), ALT level was 835 IU/L, alkaline

Table 1 Results of various clinical parameters during 1st episode of admission

Clinical parameters	Day of admission																	
	1	**2**	**3**	**4**	**5**	**6***	**7**	**9**	**10**	**11****	**13**	**14**	**16**	**19**	**21**	**31**	**52**	**80**
WBC ($\times 10^9$/L)	5.6	7.6	6.7	10.0	14.8	22	15.7	1.8	2.2	1.2	0.3	0.5	1.0	1.3	1.8	4.2	9.5	7.0
Neutrophil ($\times 10^9$/L)	1.5	–	1.1	0.6	–	–	–	–	–	0.8	–	0.1	–	–	0.2	2.9	4.8	3.0
Platelet ($\times 10^9$/L)	91	61	33	21	15	24	40	43	25	41	38	34	179	533	773	448	624	419
Urea (mmol/L)	4.7	2.9	3.2	4.5	5.7	4.7	6.1	14.2	18.4	14.8	3.0	3.7	7.4	7.4	6.8	4.1	5.8	0.9
Creatinine (μmol/L)	26	25	20	25	20	23	24	46	75	70	30	31	45	28	24	29	29	29
Total bilirubin (μmol/L)	22	12	15	74	87	139	228	284	237	192	155	165	148	106	–	27	10	6
Direct bilirubin (μmol/L)	–	–	–	–	–	–	209	272	219	168	–	132	129	93	–	18	–	–
ALT (IU/L)	69	127	189	312	390	725	766	365	265	259	268	223	137	121	–	74	71	30
Ammonia (μmol/L)	–	35	-	40	–	77	105	39	25	–	–	32	44	–	–	–	–	–
pH	–	7.4	7.37	7.4	7.37	7.41	7.5	7.47	7.34	7.05	7.43	7.48	7.44	7.42	–	–	–	–
HCO_3 (mmol/L)	–	20	17	16	17	20	25	26	15	6	22	24	24	25	–	–	–	–
Lactate (mmol/L)	–	3.1	7.5	8.5	12.1	15.4	14.1	–	14.9	26.7	2.6	2.7	2.0	1.6	1.2	1.8	3.2	–
PT (second)	–	11.7	–	26	32	24	40	15	34	17.2	11.8	11.4	11.6	–	–	9.3	9.6	–
INR	–	1.15	–	2.69	3.36	2.47	4.27	1.5	3.59	1.73	1.16	1.11	1.14	–	–	<1.0	<1.0	–
APTT (second)	–	31.6	–	58	70	102	93.4	39	47	37.8	32.9	29.1	27.3	–	–	24.4	24.1	–

WBC=white blood cell; ALT=alanine transaminase; HCO_3=bicarbonate; PT=prothrombin time; INR=international normalised ratio; APTT=activated partial thromboplastin time

*Immunotherapy had been started since Day 6; **whereas CRRT was started on Day 11.

phosphatase (ALP) level was 250 IU/L (Normal: 124–341 IU/L), aspartate transaminase (AST) level was 2381 IU/L (Normal: <79 IU/L) and gamma-glutamyl transpeptidase (GGT) level was 179 (Normal: 15–132 IU/L). The ammonia level was 99 µmol/L (Normal: 21-50 µmol/L).

Four days after starting chemotherapy, she suddenly deteriorated with tachypnoea, desaturation and skin mottling. She required intubation for ventilatory support. Investigations revealed urea 18.4 mmol/L (Normal: 1.4–6.8 mmol/L) and creatinine 75 µmol/L (Normal: <37 µmol/L), blood gas pH 7.34 with bicarbonate 15 mmol/L (Normal: 22–26 mmol/L) and base excess -8.9 mmol/L (Normal: -2–2 mmol/L). Markedly increased lactate 14.9 mmol/L and pyruvate 542 µmol/L (Normal: 50–145 µmol/L) were noted. The vancomycin trough level was also elevated at 25.8 mg/L (Normal: 5–10 mg/L).

Cyclosporin A and vancomycin were therefore stopped. Regular bicarbonate and fruosemide infusion were administered. The lactate level kept rising to a peak level of 26.7 mmol/L with blood gas pH 7.05 and bicarbonate 6 mmol/L. She also developed fluid overload despite a satisfactory urine output (around 4 ml/kg/hour). Her weight increased from 4.73 kg to 5.68 kg (20.1% increase) and CRRT was then decided.

A continuous arteriovenous haemofiltration (CAVH) circuit using Haemofilter FH22 and neonatal lines was started. She achieved a mean ultrafiltration rate of 33.03 ml/kg/hour, and the maximal ultrafiltration rate was 52.85 ml/kg/hour. The urea, creatinine, lactate and vancomycin level all dropped gradually after initiation of continuous renal replacement therapy (CRRT) (Figure 1). Post-CRRT blood sampling revealed urea 1.9 mmol/L, creatinine 25 µmol/L, lactate 2.1 mmol/L, blood gas pH 7.43, base excess 0.6 mmol/L and vancomycin level <2.0 mg/L. The urea reduction rate was 84.92%. Her body weight also reduced to 4.73 kg (16.7% reduction). CRRT was given for 48 hours in view of successful correction of fluid overload, acidosis and the lowering of level of toxic metabolites.

She was then gradually stabilised with all parameters normalised. No positive infectious cause could be identified and lumbar puncture after disease stabilisation confirmed no central nervous system involvement. However, repeated bone marrow examination still showed evidence of haemophagocytosis with markedly depressed granulopoiesis, probably due to previous dose of etoposide. Therefore etoposide was not continued.

Her hepatosplenomegaly resolved gradually. Monitoring of disease activity including cell count and liver function also showed promising results. Fibrinogen rose gradually to peak value of 1.94 g/L, and ferritin decreased to a lowest level of 167 pmol/L. Cyclosporin A was stopped 14 weeks after admission. Cocktail vitamins, carnitine and coenzyme Q supplement were stopped two months after admission. She was maintained on usual feeding with no metabolic decompensation. She was eventually discharged after 85 days of hospitalisation and remained in good general condition.

However, two weeks after her discharge, her disease relapsed. Similarly, she presented with fever without localising symptoms. Abdominal examination showed a mild hepatomegaly palpable at one centimeter below the right costal margin, the spleen was not palpable on admission. Investigations on admission showed normal complete blood picture with mildly elevated ALT 54 IU/L and C-reactive protein 21.4 mg/L. Evolving hepatosplenomegaly and pancytopenia with deranged liver function and clotting profile developed after admission.

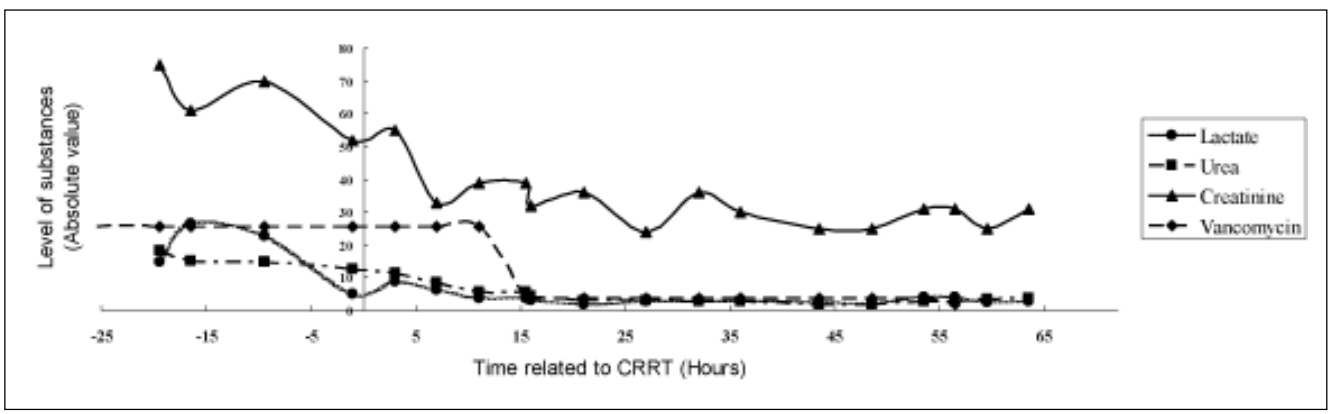


Figure 1 Serial level of various substances in first continuous renal replacement therapy (CRRT).

Besides, the lactic acidosis recurred (first lactate after admission 8.6 mmol/L at blood gas pH 7.33, bicarbonate 15 mmol/L and base excess -9.4 mmol/L). Ferritin level was again elevated to 3341 pmol/L and fibrinogen level was reduced to 0.99 g/L. Fasting triglyceride was 3.0 mmol/L. Bone marrow aspiration performed three days after admission showed an increase in histiocytes and a significant proportion showed haemophagocytic activities. Cerebrospinal fluid cytology showed no central nervous system involvement. Extensive search for possible disease-triggering infectious agents was carried out and no conclusive causative agent could be identified.

Immunotherapy including cyclosporin A, etoposide and dexamethasone was initiated promptly after confirmation of relapse. However, her condition deteriorated and required intubation for ventilatory support one week after admission. Refractory lactic acidosis was noted again despite continuous bicarbonate infusion. Peak lactate level was 21.5 mmol/L after admission. CAVH was commenced again. The process was smooth and satisfactory ultrafiltration was achieved during total 41 hours of therapy. Urea reduction rate was 67.3% with post-CRRT lactate 2.6 mmol/L. Her condition was gradually stabilised, and the liver function improved. There was no rebound of lactic acidosis. After completing the initial phase of treatment, she was started on continuation phase of treatment according to the treatment protocol.

Owing to the early relapse of the disease, she was referred to a local bone marrow transplant (BMT) center. However, she experienced central nervous system disease involvement soon after referral as evidenced by lymphohistiocytic infiltrate from cerebrospinal fluid and diffuse parenchymal and leptomeningeal enhancing lesions in magnetic resonance imaging brain examination. Reviewing the laboratory results and summaries does not find evidence of recurrent lactic acidosis nor requirement of CRRT after her referral to the BMT unit. Double unit cord blood transplant was eventually performed seven months after her first presentation. Unfortunately she suffered from severe complications related to BMT, namely veno-occlusive disease, graft versus host disease and superimposed sepsis, and eventually succumbed nine months after her presentation.

Discussion

Haemophagocytic lymphohistiocytosis (HLH) is an uncommon disease with high mortality. The reported overall mortality ranged from 22% to 57%.[1-5] The diagnosis can be established according to Hemophagocytic Lymphohistiocytosis Study Group treatment protocol 2004[6] (Table 2). The initial presentation may be non-specific and easily confused with sepsis, particularly in young patients.

HLH can be further divided into primary and secondary HLH. Primary HLH includes familial HLH (FHLH) and those with underlying immune deficiency. FHLH is an autosomal recessive or X-linked disease that tends to present as typical and recurrent HLH in early infancy. Several known genetic mutations are associated with the FHLH,

Table 2 Diagnostic guidelines for haemophagocytic lymphohistiocytosis (HLH-2004)

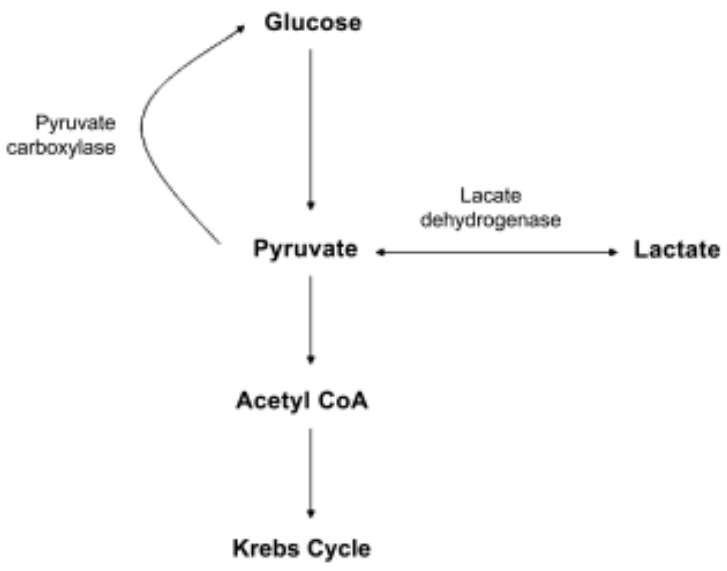
1) Molecular diagnosis consistent with haemophagocytic lymphohistiocytosis (HLH)
2) Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below)
Fever
Splenomegaly
Cytopenia (Affecting ≥2 of 3 lineages in the peripheral blood)
• Haemoglobin (<90 g/L); Platelet (<100×10^9/L); Neutrophils (<1.0×10^9/L)
• In infant <4 weeks: Haemoglobin <100 g/L)
Hypertriglyceridaemia and / or hypofibrinogenaemia
• Fasting triglyceride ≥3.0 mmol/L (≥265 mg/dL)
• Fibrinogen ≤1.5 g/L
Haemophagocytosis in bone marrow or spleen or lymph nodes
• No evidence of malignancy
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 microgam/L
Soluble CD 25 (soluble IL-2 receptor) ≥2400 U/ml

namely the perforin (PRF1), Munc13-4 (UNC13D), (syntaxin 11) STX11 and an unidentified gene on chromosome 9. The immune deficiency syndromes associated with HLH include Chediak-Higashi syndrome, Griscelli syndrome and X-linked lymhoproliferative syndrome. Secondary HLH develops due to immunological activation by various agents. Numerous infection have been found to associate with reactive HLH, however, infection can also trigger primary HLH. Viral infection such as the herpesviruses family, parvovirus, adenovirus, human immunodeficiency virus (HIV) and even H5N1 avian influenza A had all associated with HLH.[6] In particular, EBV-associated HLH accounted for majority of infection-triggered HLH: up to 37.5% of cases had been reported in a Taiwanese cohort.[2] Intracellular bacteria and rarely fungal infection had also been reported.[7] Other causes of reactive HLH include malignancy, autoimmune disease or rarely metabolic disease. Extensive workup for underlying causes should always be performed for HLH in a teenager or adult. Though we failed to perform genetic analysis for the patient due to unavailability of the test locally, our patient is probably suffering from primary HLH owing to her early onset disease with recurrence, negative family history and that no secondary cause could be identified.

Most of the organ systems would be affected in HLH due to high level of cytokines released from lymphocytes and macrophages, together with the defective cytotoxic T-cell and natural-killer (NK) cell function. Hepatic and haematological involvements almost occur in all patients,[2,3] renal complication including acute kidney injury requiring haemodialysis is observed in 30-50% of affected patients.[8] Cardiovascular, respiratory and neurological involvements are also commonly encountered. In our patient, she presented with rapidly progressing pancytopenia, disseminated intravascular coagulation, respiratory, liver and renal failure. However, one severe complication that deserves attention was severe lactic acidosis during active disease.

Lactate is produced from glycolysis under anaerobic conditions. Figure 2 illustrates its synthesis and relation with pyruvate. Liver is the main organ responsible for lactate metabolism (50%), whereas kidney accounts for about 20% of its metabolism.[9] Therefore, both hepatic and renal failure may alter lactate clearance leading to lactic acidosis.

Lactic acidosis is classified into type A that is associated with decreased perfusion and tissue hypoxia, and type B that is not due to tissue hypoxia[10] (Table 3). Steady blood lactate level is maintained through balance between lactate production and clearance. Increased production occurs not only in hypoxia such as shock and severe anaemia, but in many other causes such as malignancy, drug intoxication or inborn error of metabolism. In fact, lactic acidosis has been reported in various malignancies, in particular



Normally glucose is converted to pyruvate in the cytosol under aerobic condition through glycolysis. One molecule of glucose will be converted to two molecules of pyruvate, accompanied by the net production of 2 moleculess of adenosine triphosphate (ATP) and 2 moleculess of reduced nicotinamide adenine dinucleotide (NADH). Pyruvate may then enter the Krebs cycle to produce more ATP through oxidation into acetyl CoA. However, in oxygen depleted situation, pyruvate will only be converted to lactate by lactate dehydrogenase (LDH), coupling the oxidation of NADH produced during anaerobic glycolysis.

Red blood cells which lack mitochondria and skeletal muscle cells which require large amount of ATP in short period primarily undergo anaerobic glycolysis for ATP production, thus producing lactate as a byproduct. After taken up by liver, lactate will then be metabolized by converting back to pyruvate, and then to glucose through gluconegenesis (The Cori cycle).

Figure 2 Lactate synthesis.

Table 3 Causes of lactic acidosis

Type A: Tissue hypoxia or decreased perfusion
• Shock, severe anaemia
Type B1: Underlying disease
• Liver failure
• Renal failure
• Malignancy
• Systemic inflammatory response syndrome
Type B2: Toxin and medications
• Alcohol: Ethanol, methanol, propylene glycol
• Biguanides: Metformin and Phenformin
• Cyanogenic compounds: Cyanide, nitroprusside
• Sulfasalazine
• Salicylates
• Propofol
• Vitamin deficiency: Thiamine and biotin
• Others: Iron, isoniazid, Linezolid, Halothane, etc.
Type B3: Inborn error of metabolism
• Glucose-6-phosphatase deficiency
• Fructose-1, 5-diphosphatase deficiency
• Pyruvate carboxylase deficiency or pyruvate dehydrogenase deficiency
• Mitochondriopathy

haematological malignancy.[11,12] Decreased lactate metabolism occurs in both liver failure and renal failure. Notably, altered lactate metabolism also contributes to elevated lactate level in patient with septic shock.[13] The metabolism of lactate in critically ill status is therefore a highly complex process.

The role of lactate in cell damage remains to be specified. However, evidences emerge to suggest that lactate itself may not be the dead-end byproduct of hypoxia.[10,14] In brain hypoxia model, lactate was found to be the utilisable and obligatory substrate for glial cells upon reoxygenation after hypoxia, instead of being detrimental as previously proposed.[15] A coupled exchanger theory describes that anaerobic glycolysis of myocardial cell during ischaemia produces both lactate and protons, leading to acidosis and increased intracellular sodium concentration, and this results in increased intracellular calcium level and promotes myocardial cell injury.[16]

Nevertheless, high lactate level had been repeatedly demonstrated as an adverse prognostic factor in both adult and paediatric population.[17-20] One study carried out in emergency department evaluated 830 adult patients with severe sepsis showed that initial serum lactate level predicted mortality independently after correction of organ dysfunction.[21] Besides, various studies on trend of lactate measurements showed that critically ill patients who managed to have their lactate level normalised were associated with better survival.[10] Hence, high lactate level, though not yet showed to be directly cytotoxic, must be viewed as an important biomarker indicating poor prognosis among critically ill patients, and serial lactate monitoring provides prognostic information and serves as an indicator of management progress.

Bicarbonate has long been the medication of choice for severe acidosis. Although rarely being a curative therapy, it is often used as a "buy-time" measure as it raises the arterial pH within a short period. However, criticism of the practice is emerging both in adult and paediatric critical care.[22,23] Lack of evidence for its effectiveness, together with its potential adverse effect, namely hyperosmolarity, delayed tissue reoxygenation and worsening of intracellular acidosis, warrant a less liberal use of bicarbonate in managing patients with metabolic acidosis.

CRRT has now been widely applied as treatment of acute kidney injury in paediatrics intensive care practice.[24] A case series comprising three paediatric HLH patients also demonstrated that CRRT has been implemented as a stabilising measure to correct the lactic acidosis by means of continuous veno-venous haemodiafiltration (CVVHDF) before the definite treatment became effective to control the disease.[25] In our patient, we employed CAVH as the treatment modality as specially-tailored equipment is required for small size patients undergoing CVVH, and technical difficulty existed in ensuring a large calibre vascular access in such small patient. However, the maximal ultrafiltration rate still reached 52.85 ml/kg/hour and 31.59 ml/kg/hour respectively in her two episodes of CRRT, which were comparable to the published case series. Besides correcting acidosis and fluid overload, CRRT may have a role in removing cytokines involved in HLH. A study carried out in Japan showed that continuous haemodiafiltration using polymethyl methacrylate membrane haemofilter (PMMA) significantly lowered cytokines TNF-α and IL-6 after 3 days of treatment in a group of reactive (secondary) HLH patients.[26] Of note, 5 out of the 8 studied patients were paediatric patients ranging from below 1 year to 15 years of age. As HLH in children remains a rare disease, further study is still required to specify the role of CRRT in management of paediatric HLH patients with renal failure.

Conclusion

In conclusion, we reported a case of aggressive HLH with rapidly declining course presenting at early infancy. HLH is a disease of high mortality and multi-organ failure is commonly encountered requiring intensive supportive treatment. Prompt recognition and diagnosis of the disease with early initiation of treatment would help improve the clinical outcome.

CRRT was showed to have successfully corrected the lactic acidosis before disease condition was stabilised in this small patient. The hepatic and renal failure together with circulatory and respiratory failure may all predispose the development of her severe lactic acidosis, which carried a worse prognosis. Close monitoring of lactate level with its appropriate treatment is therefore recommended.

References

1. Imashuku S, Uedo I, Teramura T, et al. Occurrence of haemophagocytic lymphohistiocytosis at less than 1 year of age: analysis of 96 patients. Eur J Pediatr 2006;164:315-9.
2. Lee WI, Chen SH, Hung IJ, et al. Clinical Aspects, Immunologic Assessment, and Genetic Analysis in Taiwanese Children with Hemophagocytic Lymphohistiocytosis. Pediatr Infect Dis J 2009; 28:30-4.
3. Karapinar B, Yilmaz D, Balkan C, Akin M, Ay Y, Kvakli K. An unusual cause of multiple organ dysfunction syndrome in the pediatric intensive care unit: Hemophagocytic lymphohistiocytosis. Pediatr Crit Care Med 2009;10:285-90.
4. Chan JSH, Shing MMK, Lee V, Li CK, Yuen P. Haemophagocytic lymphohistiocytosis in Hong Kong children. Hong Kong Med J 2008;14:308-13.
5. Ho MH, Cheuk DK, Lee TL, Ha SY, Lau YL. Haemophagocytic lymphohistiocytosis in Hong Kong children have a wider clinical spectrum. Hong Kong Med J 2008;14:503.
6. Henter JI. Treatment protocol of the Second International HLH Study 2004. Hemophagocytic Lymphohistiocytosis Study Group 2004.
7. Rouphael NG, Talati NJ, Vaughan C, Cunningham K, Moreira R, Gould C. Infections associated with haemophagocytic syndrome. Lancet Infect Dis 2007;7:814-22.
8. Alexandre K. What nephrologists need to know about hemophagocytic syndrome. Nat Rev Nephrol 2009:329-36.
9. De Backer D. Lactic acidosis. Intensive Care Med 2003;29:699-702.
10. Vernon C, LeTourneau JL. Lactic acidosis: Recognition, Kinetics and Associated Prognosis. Crit Care Clin 2010;26:255-83.
11. Doolittle GC, Wurster MW, Rosenfeld CS, Bodensteiner DC. Malignancy-induced Lactic Acidosis. South Med J 1988;81: 533-6.
12. Cheng JC, Esparza SD, Knez VM, Sakamoto KM, Moore TB. Severe lactic acidosis in a 14-year-old female with metastatic undifferentiated carcinoma of unknown primary. J Pediatr Hematol Oncol 2004;26:780-2.
13. Levraut J, Ciebiera JP, Chave S, et al. Mild hyperlactatemia in stable septic patients is due to impaired lactate clearance rather than overproduction. Am J Respir Crit Care Med 1998;157: 1021-6.
14. Gladden LB. Lactate metabolism: a new paradigm for the third millennium. J Physiol 2004;558:5-30.
15. Schurr A, Rigor BM. Brain anaerobic lactate production: A suicide note or a survival kit? Dev Neurosci 1998;20:348-57.
16. Allen DG, Xiao SH. Role of the cardiac Na^+/H^+ exchanger during ischemia and reperfusion. Cardiovasc Res 2003;57:934-41.
17. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med 2007;33:970-7.
18. Duke TD, Butt W, South M. Predictors of mortality and multiple organ failure in children with sepsis. Intensive Care Med 1997; 23:684-92.
19. Duke T. Dysoxia and lactate. Arch Dis Child 1999;81:343-50.
20. Duke TD, Butt W, South M, Karl TR. Markers of major adverse events in children after cardiac surgery. J Thorac Cardiovasc Surg 1997;114:1042-52.
21. Mikkelsen ME, Miltiades AN, Gaieski DF, et al. Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock. Crit Care Med 2009;37:1670-7.
22. Forsythe SM, Schmidt GA. Sodium Bicarbonate for the Treatment of Lactic Acidosis. Chest 2000;117:260-7.
23. Ammari AN, Schulze KF. Uses and Abuses of Sodium Bicarbonate in the Neonatal Intensive Care Unit. Curr Opin Pediatr 2002;14:151-6.
24. Goldstein SL. Overview of pediatric renal replacement therapy in acute kidney injury. Seminar in Dialysis 2009;22(2):180-4.
25. DiCarlo J, Lui WY, Frankel L, Howell W, Schiffman J, Alexander S. The hemophagocytic syndrome: titrating continuous hemofiltration to the degree of lactic acidosis. Pediatr Hemato Oncol 2006;23:599-610.
26. Tateishi Y, Oda S, Sadahiro T, et al. Continuous hemodiafiltration in the treatment of reactive hemophagocytic syndrome refractory to medical therapy. Transfus Apher Sci 2009;40:33-40.