

Case Report

Macrophage activation syndrome – a physician’s nightmare: A case report on a life-threatening complication of adult-onset Still’s disease

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Introduction

Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening condition characterized by uncontrolled immune system activation. Though it has been observed mostly among paediatric populations, it can affect patients of any age [1] HLH could be either primary (inherited) or secondary to a severe infection, malignancy, or rheumatologic condition [2]. Secondary HLH is also referred to as reactive haemophagocytic syndrome (RHS) [3]. Differentiating primary and secondary HLH has become increasingly difficult nowadays as new genetic causes are identified and patients who develop secondary forms of HLH are found to have some genetic aetiology as well [4]. Many elements of the immune system play important roles in the pathogenesis of HLH including macrophages, natural killer (NK) cells, cytotoxic lymphocytes and toll-like receptors (TLR). Macrophage activation syndrome (MAS) is a subset of HLH that occurs in patients with juvenile idiopathic arthritis (JIA) and other rheumatologic diseases [1]. The onset of MAS is usually acute. Patients develop sudden onset of non-remitting high-grade fever associated with hepatosplenomegaly, lymphadenopathy, cytopenia and liver transaminitis. Triglyceridaemia, elevated lactate dehydrogenase and hyponatraemia are also commonly observed. Coagulation abnormality with prolonged INR and APTT, hypofibrinogenaemia and the presence of fibrin degradation products are also seen [5].

Still’s disease is systemic onset JIA (sJIA), one of seven major types of JIA and accounting for 5-15% of all JIA [6,7]. It is an inflammatory disorder due to dysregulation of the innate immune system but, surprisingly, lacking autoreactive T cells and autoantibodies. It is characterized by arthritis, quotidian fever, evanescent erythematous rash, generalized lymphadenopathy, serositis and hepatomegaly and/or splenomegaly. Laboratory abnormalities include anaemia, leukocytosis, thrombocytosis, high ESR & CRP and elevated serum ferritin [7] Stills disease is known to occur in adults as well, called adult-

onset Still's disease (AOSD) [8]. AOSD occurs worldwide, usually affecting young adults with a median age at diagnosis of around 36 years. There is no clear consensus on the sex ratio of affected patients [9]. Aetiology of AOSD is not fully understood. Some studies suggest a potential role for genetic factors. Many non-genetic triggers are also identified such as a large number of viruses, some bacteria and solid and haematological malignancies [10].

AOSD is diagnosed clinically. There is no definitive diagnostic test which means that the diagnosis relies on exclusion of a vast range of potential mimickers such as autoimmune, malignancy and other autoinflammatory diseases [11] MAS complicating AOSD had been well documented [9,10,12]. It has been speculated that AOSD and MAS may be part of the same disease spectrum, in which AOSD is the milder form [10]. Changes in laboratory features are observed during the onset of MAS in the background of sJIA and these changes include a drop in blood cell counts and ESR, marked anaemia and a rise in liver transaminases and serum bilirubin [13].

Rapid evaluation is necessary, and treatment should be started as soon as possible in this context. The major reason for adverse outcomes in MAS is the delay in diagnosis due to the relative rarity of this syndrome, its varying spectrum of clinical presentation and lack of specific laboratory findings [1].

Case presentation

A 19-year-old, school going girl without any significant past medical issues was admitted with fatigue and aching type of pain of bilateral lower limbs of two weeks duration. She also had lower back pain of one month's duration. She admitted to having significant loss of appetite over the previous week. She denied any history of fever. She did not have a sore throat or any respiratory symptoms. She admitted to having dyspeptic symptoms and nausea but denied episodes of vomiting or altered bowel habits. Her urine output was normal and she did not have any urinary symptoms. She did not have features of central nervous system infection. She did not have chest pain but had palpitations. She did not give a history of drenching sweats or bony pain. She denied a history of trauma. History also excluded any preceding diarrhoeal or respiratory illness. She did not have high risk sexual behaviour that put her at risk for sexually transmitted diseases or any occupational risk factors for blood transmitted diseases. Symptoms of age related malignancies or underlying autoimmune connective tissue disease were negative. She did not have any risk factors for familial autoimmune, metabolic or malignant conditions.

On examination, she was afebrile but pale and icteric. Blood pressure was 80/53mmHg with a pulse rate of 80 beats per minute. Oxygen saturation on room air was 96%. She was also found to have a generalized, non tender lymphadenopathy. Lung auscultation revealed bilateral lower zone fine crepitations. Jugular venous pressure was not elevated and cardiac auscultation was normal. She did not have any focal neurological signs or sensory impairment. There was no spinal tenderness. She was given intravenous (IV) fluid boluses and started on IV noradrenaline. Her blood investigations showed pancytopenia, an elevated C-reactive protein (CRP) and a remarkably low erythrocyte

sedimentation rate (ESR). Liver function tests (LFT) were altered with transaminitis and hypoalbuminaemia. Lactate dehydrogenase (LDH) was significantly elevated. Renal function tests (RFT) and urine analysis were normal. (Table 1) Cultures were taken and she was started on IV ceftriaxone 1g b.i.d, oral clarithromycin 500mg b.i.d and oral doxycycline 100mg b.i.d. Cultures turned out to be negative. Chest x-ray (CXR) showed bilateral mild pleural effusion with air space shadowing. Ultrasonography (USS) of abdomen showed hepatomegaly with multiple enlarged lymph nodes in bilateral inguinal region and tiny para-aortic lymphadenopathy. Urgent contrast enhanced computed tomography (CECT) of abdomen and pelvis was planned but postponed due to the unstable condition of the patient. Two-dimensional echocardiogram (2D Echo) was normal. On day 3, she started to develop high spiking fever episodes not responding to anti-pyretics. Repeated blood investigations showed worsening of pancytopenia, liver transaminitis and an altered coagulation profile. (Table 1) CECT showed multiple lymphadenopathies and splenomegaly. Inguinal lymph node biopsy was done on day 3 after correction of coagulability abnormalities. Fever continued to persist and IV antibiotics were switched to IV meropenem. Serum ferritin was high as was the fasting triglyceride level. Blood picture did not show features of HLH. However, IV dexamethasone 4mg q.d.s was started. Despite the empirical treatment, she deteriorated and became drowsy and confused. NCCT/Brain was normal. On day 10 she was transferred to the medical intensive care unit where she was electively intubated. Lymph node biopsy showed features consistent with HLH. An urgent bone marrow biopsy was done and the diagnosis of HLH was confirmed. She was given IV methyl prednisolone pulses (500mg daily) and oral cyclosporin 50mg daily. Despite the best efforts of the medical team, she succumbed on day 12.

Table 1. Summary of investigations

Investigations	Days since first admission					
	D-12#	D1	D3	D6	D9	D12
WBC (/μL) (4-11)	5.94	2.76	2.62	3.27	5.28	5.66
N (%)	-	71.7	74.0	75.8	68.2	77.3
L (%)	20.2	21.4	21.8	19.9	24.8	15.4
M (%)	-	6.5	4.2	4.3	7.0	7.1
E (%)	-	0	0	0	0	0
Hb (g/dL) (11.0-16.0)	11.2	10.7	8.4	7.6	7.6	7.4
Plt (/μL) (150-450)	153	73	60	70*	52	33
ALT (U/L) (16-63)	-	222	150	165	227	441
AST (U/L) (15-37)	-	591	444	-	531	1356
ALP (U/L) (46-116)	-	733	450	-	-	-
TP (g/L) (64-82)	-	45	37	50	-	45
Alb (g/L) (34-50)	-	19	19	31	-	23
Glo (g/L) (22-48)	-	26	17	19	-	22
TB	-	-	113	183	147	212
DB	-	-	106	166	142	168
Na (mmol/L) (136-145)	-	132	131	132	-	147
K (mmol/L) (3.5-5.1)	-	5.0	3.4	2.3	-	5.0
Ca (mmol/L) (2.10-2.54)	-	2.12	-	-	-	-

BU mmol/L (2.5-6.4)	-	6.0	2.8	3.2	-	8.2
SCr μ mol/L (62-115)	-	61	51	64	-	-
ESR mm/1st hour	-	04	05	10	-	-
CRP (mg/L) (0-3)	-	48	34	-	-	3.2
INR	-	1.3	1.8	1.6	1.6	1.2
LDH (U/L) (120-246)	-	2434	2621	-	-	-
SF (ng/ml) (6.24-137)	-	-	>1000	-	-	-
TC (mmol/L) (<5.18)	-	-	-	4.28	3.85	-
TG (mmol/L) (<1.7)	-	-	-	22.92	17.76	-
HDL (mmol/L) (>1.55)	-	-	-	0.18	0.20	-
Troponin I (0-0.15)	-	0.014	1.710	0.166	-	-
Blood culture D1 D4 & D9	Coagulase negative staphylococcus species isolated No growth					
Urine culture D4 D8 D11	No growth Candida species (low colony count) Heavy mixed growth					

WBC, white blood cells; N, neutrophils; L, lymphocytes; E, eosinophils; Hb, haemoglobin; Plt, platelets; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; TP, total protein; Alb, albumin; Glo, globulin; TB, total bilirubin; DB, direct bilirubin; Na, sodium; K, potassium; Ca, calcium; BU, blood urea; SCr, serum creatinine; ESR, erythrocyte sedimentation rate; CRP, c-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; SF, serum ferritin; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; Dx, days since first admission

- Investigations done at a local facility 12 days prior to admission

* - Platelets were transfused on the previous day

Table 2. Summary of special investigations

Blood picture D1	Findings are in favour of DIC possibly due to underlying infection/Inflammation
Bone marrow biopsy D12	Appearances are consistent with haemophagocytic syndrome
Inguinal lymph node biopsy D5	Marked paracortical and sinus expansion with histiocytes that show occasional haemophagocytosis
Rotational thromboelastometry (ROTEM) D3	Moderate to severe coagulation factor deficiency and fibrinogen factor deficiency/dysfunction
Rheumatoid factor	<30 IU/ml (<30)

Discussion

Although there are many proposed diagnostic criteria for AOSD, Yamaguchi criteria and Fautrel's set of diagnostic criteria are commonly used. Fautrel's set of diagnostic criteria is more specific but requires measurement of glycosylated ferritin which is not widely available. Application of Yamaguchi criteria is hindered by the need to exclude a large number of mimicking clinical conditions. Nevertheless, it is considered more sensitive than Fautrel's set of diagnostic criteria and widely used [11,14].

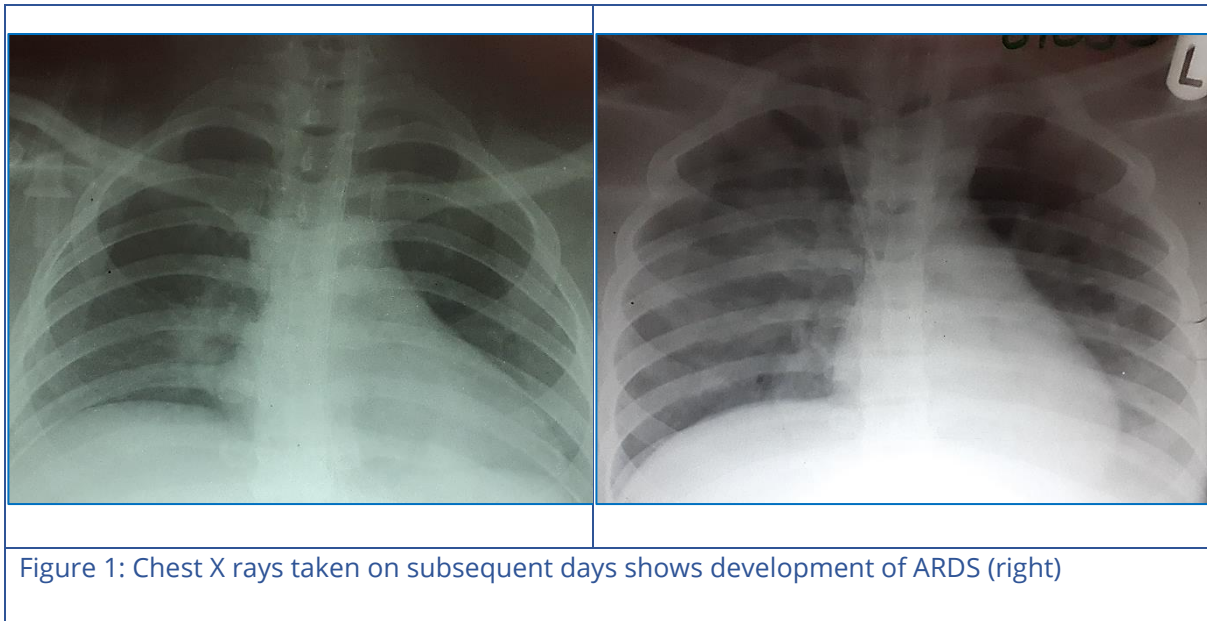
This patient had already developed MAS on admission, thus making the application of diagnostic criteria difficult. MAS causes cytopenia and a low ESR, in contrast to ASOD

which is characterized by neutrophil leucocytosis and an elevated ESR [7,13]. She still fulfilled the Yamaguchi criteria by having two major criteria (fever $\geq 39^{\circ}\text{C}$ lasting more than one week & arthralgia or arthritis, lasting ≥ 2 week), three out of four minor criteria (recent development of significant lymphadenopathy, hepatomegaly or splenomegaly, abnormal liver function tests & negative tests for antinuclear antibody and rheumatoid factor) and by satisfying the exclusion criteria (negative bone marrow and lymph node biopsy for malignancies, negative CECT abdomen and pelvis for solid organ malignancies and unlikelihood of other rheumatic diseases as evident from clinical examination and negative serology) [15]. Fautrel's set of diagnostic criteria could not be fulfilled, mainly due to the onset of MAS and lack of laboratory facilities to measure glycosylated ferritin [16].

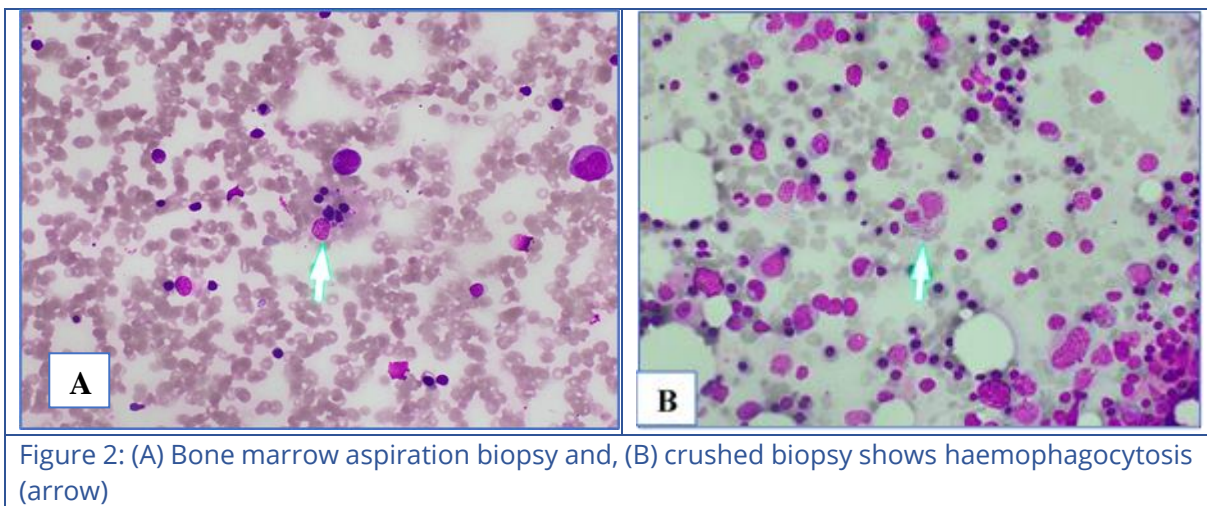
The diagnosis of MAS is based on criteria that include clinical, biochemical and imaging components [17]. This patient satisfied the criteria for the diagnosis of MAS by having six out of eight criteria including fever, splenomegaly, cytopenias affecting all three lines, hypertriglyceridemia & hypofibrinogenemia and ferritin >500 mg/L. NK-cell activity and soluble CD25 level could not be assessed due to lack of laboratory facilities. (Table 1)

HScore is a scoring system developed by Fardet et al. in 2014 for the diagnosis of RHS. The best cut off value for the HScore was determined to be 169 with a sensitivity and specificity of 93% & 86% respectively and 90% accuracy [18]. Our patient had a score of 254, corresponding to $>99\%$ of probability of MAS.

Central nervous system (CNS) dysfunction has been frequently observed in MAS. Patients may become lethargic, irritable, disorientated, complain of headache, develop seizures or go into coma. Renal, pulmonary, and cardiac involvement has been also reported [5]. This patient showed signs of CNS dysfunction and went into coma on day 10. She also developed pulmonary and cardiac complications as evidenced by the bilateral lung shadows and low BP coupled with transient sinus pauses and elevated troponin I although she had a normal 2D echo. (Table 1) (Figure 1) Respiratory complications may require ventilatory support and could result in death from acute respiratory distress syndrome (ARDS) [1] as in this case.



The pathognomonic feature of MAS is numerous well-differentiated macrophages actively phagocytosing hematopoietic cells in a bone marrow biopsy. These cells can be found in other organs as well [5]. In our case, haemophagocytic activity was seen in both the bone marrow and in the lymph node biopsies. (Figures 2-4)



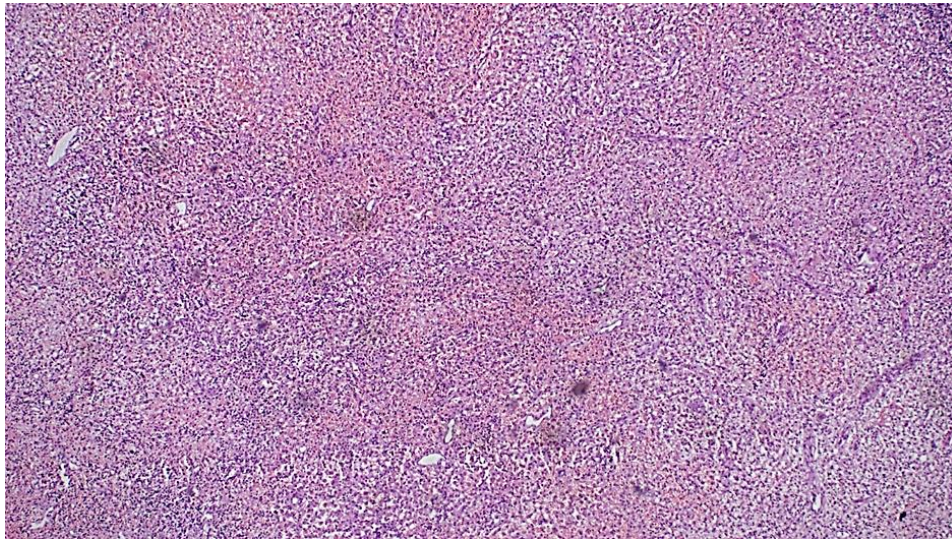


Figure 3: Light microscopy of lymph node biopsy shows marked paracortical and sinus expansion with histiocytes

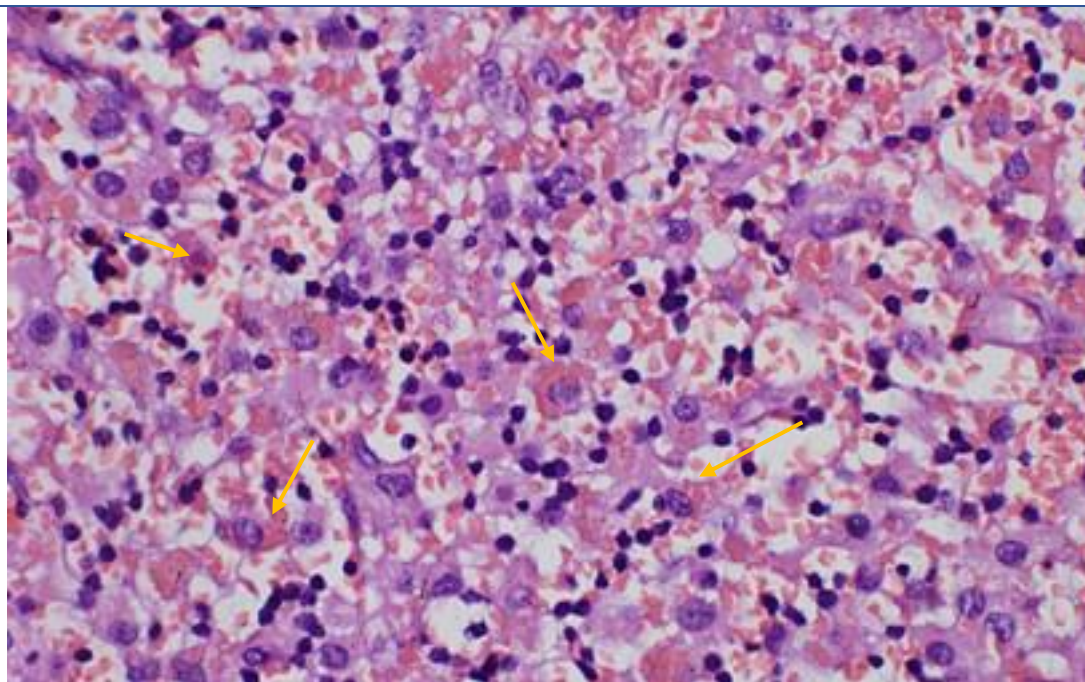


Figure 4: Haemophagocytosis in lymph node biopsy

The aim of treatment is to suppress uncontrolled inflammation by destroying immune cells [19]. Recommended treatment, based on the HLH-94 protocol consists of eight weeks of induction therapy with etoposide and dexamethasone. For intrathecal therapy, which is reserved for CNS involvement, intrathecal methotrexate (MTX) is recommended [20,21]. Some clinicians add intrathecal hydrocortisone to MTX for CNS disease as studied in the HLH-2004 trial [19].

MAS shows a good response to the treatment of any underlying condition which may allow the patient to avoid HLH-specific therapy [19] Corticosteroids are the mainstay of

treatment of AOSD. Though disease modifying anti rheumatoid drugs (DMARDs) also have a role, they are usually used in steroid dependent patients and there is very limited data on efficacy of any particular DMARD [22]. So, in the context of MAS complicating AOSD, which was the case in this patient, the treatment for MAS would have addressed the AOSD as well.

In our patient, we started IV dexamethasone 4mg q.d.s. Etoposide was not administered as it was not available in hospital. Although she developed CNS symptoms later in the course of the illness, the altered coagulation profile resulted in a delay in using intrathecal medications. She was also started on oral cyclosporin, despite the fact that the use of cyclosporin (CSA) in the induction period did not improve the outcome in HLH-2004 regime. According to some studies, CSA was beneficial in rheuma-associated HLH/macrophage activation syndrome [20].

Alemtuzumab could be used as an alternative to etoposide in patients with liver disease. Patients should be managed in intensive care units with neutropaenic precautions. Prophylaxis for *Pneumocystis jirovecii* (oral co-trimazole) and fungal organisms should be given to all patients. Intravenous immune globulin (IVIG) could be considered for patients with immunodeficiency. Indications for allogeneic hematopoietic cell transplant include HLH gene mutations, poor response to HLH induction therapy, CNS disease and haematological malignancy [19]. Mortality rates are high (5-39%) if MAS is left untreated. (23) Patients treated with the HLH-94 protocol were found to have an improved outcome with a 5-year probability of survival of 54% ± 6% [20].

Conclusion

MAS is a life-threatening complication of AOSD that requires early recognition and prompt treatment. Despite advancements in medicine and ground-breaking clinical trials that helped to develop effective treatment protocols, mortality rates remain high.

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