CASE REPORT

Haemophagocytic lymphohistiocytosis associated with *Mycobacterium tuberculosis* infection

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SUMMARY

Haemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal condition that can be primary or secondary. Secondary HLH can occur in association with infections, most commonly viral infections, but has also been reported in association with *Mycobacterium tuberculosis* (TB). Prompt identification of the underlying cause of HLH is important as it guides treatment decisions. Early initiation of appropriate treatment (eg, anti-TB treatment) reduces morbidity and mortality. We present a case of HLH associated with TB infection. Initial TB investigations were negative and standard combination chemoimmunotherapy for HLH resulted in a limited clinical response. On apparent relapse of HLH, further investigation revealed TB with changes on CT chest, granuloma on bone marrow and eventual positive TB culture on bronchoalveolar lavage. Subsequent treatment with quadruple anti-TB treatment resulted in rapid clinical response and disease remission. We advocate continued monitoring for TB infection in patients with HLH, and prophylaxis or full treatment for those at high risk.

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a rare, potentially fatal condition in which abnormal activation of the immune system results in haemophagocytosis, inflammation and tissue damage. This results in a variety of signs and symptoms but most commonly fever, lymphadenopathy, splenomegaly, cytopenias, hyperferritinaemia and hypertriglyceridaemia.

HLH can be either primary (familial) or secondary (sporadic, acquired). Secondary HLH can occur in association with infections, most commonly viral infections, but has also been associated with fungal, parasitic and bacterial infections, including *Mycobacterium tuberculosis* (TB).^{1–3}

HLH carries a high mortality rate if untreated or treatment is initiated late in the disease process; so early initiation of treatment, even while awaiting confirmation of the diagnosis, is recommended if there is high clinical suspicion.⁴ Furthermore, early treatment in limiting disease progression and the risk of irreversible tissue damage can increase chances of achieving a good response to treatment.⁵ Prompt identification of the underlying cause of HLH is also important as it guides treatment decisions, particularly in non-viral infection-associated HLH, which often responds to treatment of the underlying infection.³

Current treatment of primary HLH follows the Histiocyte Society HLH-2004 treatment protocol,

which can also be beneficial for patients with secondary HLH.⁵ This consists of a combination of chemoimmunotherapy agents. However, in cases of secondary HLH in association with non-viral infections, targeted treatment of the infection can be effective in treating the disorder by removing the stimulus for the activation of the immune system. Therefore, early initiation of the appropriate treatment (eg, anti-TB treatment) can reduce morbidity and mortality. A patient may also be able to avoid prolonged treatment with the standard chemoimmunotherapy agents with their associated adverse effects.

We present a case of HLH associated with TB infection. Initial investigations were negative for TB, although a short course of TB treatment was given while investigations were ongoing. Standard combination chemoimmunotherapy for HLH resulted in a limited clinical response and ultimate return of symptoms attributed to HLH. Reinvestigation for the cause of the patient's symptoms and an increasing suspicion of TB, led to initiation of empiric treatment with a full course of quadruple anti-TB therapy resulting in rapid clinical response and disease remission. Investigations (PCR and culture) subsequently confirmed the diagnosis of TB.

While the negative tests on presentation prevent confirmation of TB as the cause of the patient's symptoms and may relate to reactivation following heavy immunosuppression, we advocate continuous suspicion of underlying infection in the management of patients with suspected HLH. Delay in treatment can increase morbidity and mortality both from HLH as well as from the treatment given, particularly if chemoimmunotherapy was not necessarily required.

CASE PRESENTATION

A 42-year-old Nepalese man presented to the accident and emergency department with a 5-day history of fevers, rigours and myalgia. He had no significant medical history and took no medications. His siblings and non-consanguineous parents were well. He was a non-smoker, a teetotaler and did not use illicit drugs. He had been a resident of the UK for 12 years and had most recently travelled to Nepal 4 months earlier; of note is the fact that he had made contact with a family member with TB in Nepal.

His baseline observations included a temperature of 38.8°C, a blood pressure of 95/52 mm Hg, a heart rate of 114/min (sinus tachycardia on ECG), respiratory rate of 20/min and oxygen saturations were 96%

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on air. Cardiovascular and respiratory examinations were unremarkable with normal jugular venous pressure, heart sounds and breath sounds with no additional sounds on auscultation. Abdominal examination, however, revealed mild splenomegaly. There was no palpable lymphadenopathy.

Initial investigations revealed normocytic anaemia, haemoglobin 77 g/L (12.5–15 g/L), raised white cell count $15.2 \times 10^9/L$ ($4.0\text{--}11.0 \times 10^9$), raised neutrophil count $13.4 \times 10^9/L$ ($2.0\text{--}7.0 \times 10^9$) and a normal platelet count of $147 \times 10^9/L$ ($150\text{--}400 \times 10^9$). Liver function tests were deranged with mildly raised bilirubin 25 mmol/L (3–17 mmol/L), raised alanine aminotransferase 48 IU/L (10–40 IU/L), raised alkaline phosphatase 372 IU/L (44–147 IU/L); however, albumin was normal at 37 g/L (30–50 g/L). Blood tests also revealed a raised ferritin 168 962 ng/mL (13–300 ng/mL), raised triglycerides 3.84 mmol/L (normal <1.7 mmol/L), raised lactate dehydrogenase 550 IU/L (140–250 IU/L) and raised C reactive protein >156 mmol/L. Renal function and clotting were preserved. A baseline septic screen was negative (chest X-ray clear, urine dipstick negative, blood cultures negative). CT scan of his chest, abdomen and pelvis revealed mediastinal lymphadenopathy and splenomegaly.

His haemodynamic instability merited rapid escalation to the intensive care unit for inotropic support. He was initially empirically treated with piperacillin/tazobactam and gentamicin with no response. He went on to have multiple courses of antimicrobials (including meropenem, teicoplanin, caspofungin, daptomycin, linezolid and ambisome) but this was of no avail. Repeated blood and urine cultures were negative. A mediastinal lymph node fine-needle aspirate (FNA) did not show evidence of lymphoma or TB; cultures were not undertaken. A peripheral blood TB ELISPOT was negative.

With fevers, splenomegaly, a progressive pancytopenia, raised ferritin and raised fasting triglyceride levels, the patient was noted to satisfy five of the eight second-line criteria required for a diagnosis of HLH.⁶ A bone marrow biopsy was therefore performed which confirmed the diagnosis, with 1 in 200 cells demonstrating haemophagocytosis.

The underlying pathoetiology for HLH was unclear and the patient underwent initial screens for both congenital and acquired causes, as outlined in table 1, which were negative.

TREATMENT

With no clear driving pathoetiology, treatment was started according to the Histiocyte Society HLH-2004 treatment protocol.⁵ He received etoposide 300 mg twice weekly, for 2 weeks. However, a subsequent worsening pancytopenia resulted in etoposide being withheld for 1 week and restarted for weeks 3 to 9. Ciclosporin was given for 8 weeks; however, this was stopped due to hepatorenal failure (creatinine peaked at 510 $\mu\text{mol/L}$, alanine transaminase 38 IU/L, alkaline phosphatase 293 IU/L) despite a 25% dose reduction. He received a full course of dexamethasone. Given the history of recent exposure to a TB positive contact in Nepal, he was also started empirically on anti-TB treatment despite no definitive evidence of TB on lymph node FNA and a negative peripheral blood TB ELISPOT. Rifampicin was omitted due to hepatorenal failure.

The patient failed to respond to first-line HLH treatment, developing worsening pancytopenia and drug-related hepatic and renal toxicity. Worsening hepatorenal failure also resulted in his anti-TB treatment being stopped after 2 weeks. The patient's clinical state deteriorated to such an extent that he required repeated admissions to intensive care unit for inotropic support and non-invasive ventilation. He became transfusion dependent

(red cells and platelets), and required G-CSF to support his neutrophil counts.

Owing to the poor clinical progress, the patient was transferred to a tertiary care centre for alternative treatment options. Following the transfer, he continued to have recurrent culture-negative fevers with persistently raised ferritin (39 805 $\mu\text{g/L}$) and triglyceride levels (8.77 mmol/L). Second-line treatment consisted of dexamethasone (20 mg once daily) and 5 days of intravenous immunoglobulin (0.4 g/kg daily) with no apparent improvement. He was then started on a 5-day course of alemtuzumab (10 mg daily) and ciclosporin (75 mg twice daily) and this resulted in clinical improvement. His fevers resolved, and there was a fall in his ferritin and triglyceride levels with associated slight improvement in his cytopenias.

He was discharged from hospital on ciclosporin and a reducing course of dexamethasone, but was readmitted 2 weeks later with fevers, sweats, myalgia, left upper quadrant pain and

Table 1 Initial negative screen for both congenital and acquired forms of HLH

Immunological screen	Infection screen
sCD255 054 pg/mL (<2500 pg/mL)	EBV PCR negative
ANA negative	CMV PCR negative (<150)
ANCA negative	Hepatitis B negative
RhF <20	Hepatitis C negative
	HIV negative
	TB ELISPOT (peripheral blood) negative
	Influenza A/B negative
	Rhinovirus negative
	Coronavirus negative
	Adenovirus negative
	Metapneumovirus negative
	Enterovirus negative
	Parechovirus negative
	Bocavirus negative
	RSV negative
	Strongyloides serology negative
	Bartonella serology negative
	Chikungunya negative
	West Nile virus negative
	Leishmaniasis negative
	Brucella negative
	Dengue negative
	Rickettsia negative
	Spotted fevers negative
	Tick-borne encephalitis negative
	Sandfly fever negative
	Mycoplasma pneumoniae negative
	Legionella pneumophila negative (serology and urinary antigen)
	Chlamydia pneumoniae negative
	Leptospira serology negative
	Antistreptolysin O titre negative
Genetic screen	Malignancy screen
HLH screen—no primary cause (no pathological mutations of PRF1, UNC13D or STX11 identified)	OGD—gastritis
	Flexible sigmoidoscopy—nil abnormal detected
	CT brain—no space occupying lesion
	CT CAP—mediastinal lymphadenopathy, splenomegaly
	MRI brain—pontine enhancement (deemed to be secondary to electrolyte disturbances during prolonged intensive care admission).
	Tumour markers—negative

ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibody; CAP, chest abdomen pelvis; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLH, haemophagocytic lymphohistiocytosis; OGD, oesophagogastroduodenoscopy; RSV, respiratory syncytial virus; TB, *Mycobacterium tuberculosis*.

pleuritic chest pain with associated shortness of breath. He had tender hepatosplenomegaly and worsening pancytopenia and he was deemed to have suffered a relapse of his HLH.

The patient began the work up for haematopoietic stem-cell transplantation as treatment for refractory HLH. He had siblings living in Nepal who were HLA-typed in preparation. His brother was found to be a positive match and was flown to the UK for stem cell collection.

The patient was also found to have cytomegalovirus (CMV) reactivation (CMV PCR 959 copies/mL compared to <150 copies/mL a week before) secondary to his immunosuppression and he was, therefore, started on ganciclovir.

In view of his respiratory symptoms on this presentation, a CT pulmonary angiogram (CTPA) and high-resolution CT (HRCT) of his chest were performed. Ground-glass shadowing and bilateral cavitating pulmonary nodules were noted. He underwent a bronchoscopy with bronchoalveolar lavage (BAL) to obtain samples for cultures and was then started on empiric quadruple anti-TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol). He also had a repeat peripheral blood TB ELISPOT that was now reactive. This prompted a re-examination of his bone marrow from his recent admission and the further cuts taken from the trephine was evidence for the non-caseating granulomatous inflammation that was now identified. He underwent a repeat bone marrow biopsy which also showed epithelioid granulomas (although ZN and PAS stains were negative). Comparison of his initial CT scans with his repeat imaging demonstrated increased mediastinal nodularity in the later scan.

Diagnosis of TB was confirmed from the BAL with positive *M. tuberculosis* complex PCR and positive TB cultures 2 weeks later.

OUTCOME AND FOLLOW-UP

Following initiation of quadruple anti-TB treatment, there was rapid clinical improvement, with resolution of his fevers and improvement to his cytopenias. He was discharged after just over 6 weeks in hospital following his second admission to the tertiary care centre (figure 1).

At discharge, he continued on quadruple anti-TB treatment, but his ciclosporin was discontinued (he received a total of 4 months treatment) and his steroids slowly weaned over a period of a month. He has been regularly followed-up in our outpatient clinic, has remained systemically well and his cytopenias have continued to gradually improve. He has had repeat CT imaging, with his most recent scan performed 6 months following discharge; this showed resolution of his mediastinal lymphadenopathy and reduction in size of the pulmonary nodules.

He completed a full course of anti-TB treatment (a total of 2 months quadruple therapy followed by 4 months of rifampicin and isoniazid as the isolate was fully sensitive). At his last clinical review (which is now 8 months following discharge), he continues to be well and his pancytopenia has resolved. He last required a blood transfusion 1 month following discharge. His most recent ferritin was 1074 µg/L at 6 months postdischarge.

DISCUSSION

HLH is a rare disorder with an estimated incidence of 1/150 000.⁶ As well as haemophagocytosis, it is characterised by fevers, lymphadenopathy, splenomegaly, cytopenias, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia, low or absent natural killer (NK) cell activity, and high-soluble CD25 (interleukin-2 (IL-2) receptor α) levels.⁵

The underlying pathophysiology is not fully understood but involves an abnormal activation of the immune system, including macrophages, NK cells and cytotoxic lymphocytes.⁶ In particular, there is failure of normal autoregulation of NK cell function, increased activation and proliferation of lymphocytes and macrophages, and increased production of cytokines, which ultimately results in uncontrolled haemophagocytosis, excessive inflammation and tissue damage.^{1 6}

HLH can be either primary (familial) or secondary (sporadic, acquired). Primary (familial) HLH, which typically affects young children, refers to HLH caused by an underlying gene mutation. The genetic defects identified affect cytotoxic T lymphocytes and NK cells, and result in dysregulation of normal function.⁷ Secondary (acquired) HLH, which can occur at any age, occurs in association with infection, malignancy (particularly T-cell lymphoma) and autoimmune disease.

Infections associated with HLH are usually viral, particularly the Epstein-Barr virus.¹ However, HLH has also been associated with bacterial, fungal and parasitic infections.^{2 3} The pathophysiology of infection-associated HLH is not fully understood but increased cytokine production, such as from Epstein-Barr virus (EBV)-infected T lymphocytes, is thought to play a role.³ In addition, it has been noted that there is an association of HLH with intracellular pathogens that typically induce Th1 immune responses, such as *M. tuberculosis*; therefore, this suggests that dysregulation of Th1 immune responses to pathogens may also play a role in triggering HLH.³

HLH carries a high mortality rate if untreated or treatment is initiated late in the disease process; so early initiation of treatment, even while awaiting confirmation of the diagnosis, is recommended if there is high clinical suspicion.⁴ Reasons for delays in initiating treatment include clinicians' unfamiliarity with the disease given its rarity, its variable clinical presentation, clinical and laboratory findings, and also the time it may take for specialised test results to come back. Furthermore, not all patients will fulfil the diagnostic criteria or may develop one of the diagnostic criteria later in the disease course.⁵

Current treatment of primary HLH follows the Histiocyte Society HLH-2004 treatment protocol, which can also be beneficial for patients with secondary HLH.⁵ However, in cases of secondary HLH, initial treatment in the form of the HLH-2004 protocol may then be adapted depending on the underlying disease.⁵ EBV-associated HLH is treated with cytotoxic chemotherapy as it can mimic T-cell lymphoma, but non-viral associated HLH often responds to treatment of the underlying infection.³ This is because treating the underlying infection may then remove the stimulus for activation of the immune system. An additional benefit in treating the triggering infection alone is that it may allow some patients to avoid the toxic side effects associated with the chemoimmunotherapy agents used in the HLH-2004 treatment protocol, such as severe immunosuppression. Haematopoietic stem cell transplantation (SCT) is a recognised curative therapy for HLH, particularly in familial HLH; however, it is associated with high treatment-related morbidity and mortality.⁸

Given the high mortality rate of HLH and the rapidity of its progression, particularly if untreated, patients should receive treatment before the diagnosis is confirmed if there is high clinical suspicion. Furthermore, early treatment can limit disease progression and the risk of irreversible tissue damage, and can increase chances of achieving a good response to treatment.⁵

M. tuberculosis is a recognised cause of HLH and a review by Brastianos *et al* 2006⁹ identified at least 37 reported cases in the English language literature, with further cases of HLH

Timeline of events

22/07/2013	Patient presented to local hospital with 5-day history of fevers, rigors and myalgia. Required transfer to ITU for inotropic support within 48 hours
05/08/2013	Diagnosed with HLH <ul style="list-style-type: none"> • Patient satisfied five of eight second line criteria required for a diagnosis of HLH: fevers, splenomegaly, a progressive pancytopenia, raised ferritin and raised fasting triglyceride levels • Bone marrow biopsy confirmed the diagnosis of HLH, with 1 in 200 cells demonstrating haemophagocytosis • Underlying patho-aetiology for HLH was unclear and the patient underwent initial screens for both congenital and acquired causes which were all negative (table 1)
05/08/2013	Started treatment for HLH in accordance with Histiocyte Society HLH-2004 treatment protocol, consisting of dexamethasone, etoposide and ciclosporin <ul style="list-style-type: none"> • Treatment complicated by worsening pancytopenia secondary to etoposide, resulting in etoposide being held for a week and restarted for weeks 3 – 9 • Treatment complicated by hepato-renal failure secondary to ciclosporin which did not respond to a dose reduction and was eventually stopped • Completed full course of dexamethasone
12/08/2013	Started empiric anti-TB treatment in light of a history of recent exposure to a TB positive contact in Nepal despite no definitive evidence of TB on lymph node FNA and a negative peripheral blood TB ELISPOT <ul style="list-style-type: none"> • Rifampicin was omitted due to hepato-renal failure
27/09/2013	Chemo-immunotherapy stopped in view of lack of clinical response (ongoing culture negative fevers and haemodynamic instability requiring repeated admissions to ITU for inotropic support and non-invasive ventilation), worsening pancytopenia, persistently raised ferritin and triglycerides, and drug-related hepatic and renal toxicity
28/09/2013	Anti-TB treatment stopped in view of worsening hepato-renal failure
17/10/2013	Patient transferred to tertiary centre for alternative treatment options
21/10/2013	Started second-line treatment for HLH consisting of dexamethasone and 5 days of intravenous immunoglobulin but with no apparent response
27/10/2013	Started alemtuzumab and ciclosporin which resulted in clinical improvement (resolution of fevers, fall in ferritin and triglycerides, slight improvement in cytopenias)
14/11/2013	Discharged from hospital on ciclosporin and a reducing course of dexamethasone
29/11/2013	Diagnosed with relapse of HLH <ul style="list-style-type: none"> • Patient re-admitted to tertiary centre with fevers, sweats, myalgia, left upper quadrant pain, pleuritic chest pain with associated shortness of breath, tender hepato-splenomegaly and worsening pancytopenia • Started work-up for haematopoietic stem-cell transplantation as treatment for refractory HLH • Also noted to have CMV reactivation secondary to immunosuppression and commenced on ganciclovir
21/11/2013	CTPA and HRCT performed in view of respiratory symptoms, which showed ground glass shadowing and bilateral cavitating pulmonary nodules <ul style="list-style-type: none"> • Comparison of patient's initial CT scans with his repeat imaging demonstrated increased mediastinal nodularity in the later scan • Increased suspicion of TB infection and HLH associated with TB infection
06/12/2013	Bronchoscopy with BAL performed to obtain samples for TB cultures and patient was then commenced on empiric quadruple anti-TB treatment
16/12/2013	Repeat peripheral blood TB ELISPOT now reactive
5/12/2013	Repeat bone marrow biopsy performed which showed epithelioid granulomas (although ZN and PAS stains were negative) <ul style="list-style-type: none"> • Re-examination of bone marrow trephine from recent admission (18/10/2013) showed evidence of non-caseating granulomatous inflammation
8/01/2014	Diagnosis of TB confirmed from the BAL with positive mycobacterium tuberculosis complex PCR <ul style="list-style-type: none"> • Positive TB cultures 2 weeks later
14/01/2014	Patient discharged from hospital <ul style="list-style-type: none"> • Rapid clinical improvement following initiation of quadruple anti-TB treatment with resolution of fevers and improvement to cytopenias • At discharge patient continued on quadruple anti-TB treatment but his ciclosporin was discontinued and his steroids slowly weaned • Under regular follow-up in the haematology outpatient clinic
19/06/2014	Completed full course of anti-TB treatment
2/07/2014	Repeat CT imaging performed showed resolution of his mediastinal lymphadenopathy and reduction in size of the pulmonary nodules
19/09/2014	Patient attended clinic for most recent review and was systemically well with complete resolution of his pancytopenia

Figure 1 Timeline of events.

associated with TB having since been reported.^{10 11} An important point highlighted by this review and subsequent case reports is that HLH associated with TB carries a high mortality (of approximately 50%) for patients not receiving any treatment or due to a delay in initiating treatment. Treatment with anti-TB treatment and chemoimmunotherapy or a combination of both improves outcomes.

This report describes a case of HLH associated with *M. tuberculosis* infection.

A negative ELISPOT and lymph node FNA suggested initial features were not related to TB. However, lymphadenopathy, fevers and splenomegaly may have reflected the disease and close contact to a patient with TB convinced initial treating physicians to include TB treatment, although this was curtailed due to toxicity. The decision that TB was not the cause of disease led to escalation of immunosuppression, which would have resulted in SCT and certain death had further extensive investigations not been performed. Whether the primary disease was TB, or whether reactivation occurred due to HLH treatment cannot be definitively determined. However, his continued response and lack of relapse of HLH following complete TB treatment leads us to suggest this may have been the primary disease.

It is notable that a negative TB ELISPOT cannot exclude a diagnosis of TB;¹² therefore, it is not useful in a high probability case and is known to be affected by immunosuppressive states. Further investigation is required if there is high clinical suspicion. In particular, culture of relevant tissues or fluids is essential. Also of interest is how useful bone marrow examination can be in diagnosing TB.¹³ Although examination of bone marrow can be useful in rapidly diagnosing TB by demonstrating granulomata, a culture for bacteria, TB and fungi is mandatory in patients presenting with fever. Without culture, antimicrobial sensitivities cannot be determined and the diagnosis cannot be confirmed. This has particular relevance for

patients from parts of the world where drug resistance is common. It is also relevant for infection control since positive microbiology from respiratory samples requires infection prevention strategies in hospital. Furthermore, TB is a statutorily notifiable disease and contact tracing must be undertaken for household contacts.

This case highlights the importance of considering TB as an infective cause of HLH and the need to have a low threshold for initiating empiric anti-TB treatment in individuals for whom there is a high clinical suspicion once the relevant clinical samples have been obtained for culture and even if confirmation of the diagnosis of TB is still pending. Delay in treatment can increase morbidity and mortality both from HLH as well as from the treatment given, particularly if chemoimmunotherapy was not necessarily required.

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Competing interests None.

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Learning points

- In patients presenting with fevers, lymphadenopathy, splenomegaly and cytopenias, particularly in association with hyperferritinaemia and hypertriglyceridaemia, a diagnosis of haemophagocytic lymphohistiocytosis (HLH) should be considered.
- If a diagnosis of HLH is suspected, investigations should be instigated not only to confirm the diagnosis, but to identify the underlying cause of HLH as this can guide treatment decisions.
- Non-viral infection-associated HLH often responds to treatment of the underlying infection.
- *Mycobacterium tuberculosis* (TB) infection is a recognised infective cause of HLH.
- If TB-associated HLH is suspected, there should be a low threshold for initiating anti-TB treatment even when confirmation of the diagnosis of TB is still pending, as early treatment can reduce morbidity and mortality.

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