MEDICAL PRACTICE

Haemophagocytic lymphohistiocytosis: an uncommon clinical presentation of tuberculosis

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Secondary haemophagocytic lymphohistiocytosis is a rare but fatal complication of tuberculosis. We describe two cases, and review the local and international experience on the management of this clinical entity. Prompt treatment with anti-tuberculous drugs forms the cornerstone of therapeutic success.

Introduction

Tuberculosis is a common notifiable infectious disease in Hong Kong; 5348 cases were notified in 2009.[1] *Mycobacterium tuberculosis* (MTB) is known as the 'great mimicker' and has a diverse range of clinical presentations. One of its rare but fatal manifestations is secondary haemophagocytic lymphohistiocytosis (HLH), which has a mortality rate of 100% in the absence of anti-tuberculous treatment.[2] Failure to consider tuberculosis in secondary HLH leads to delayed initiation of appropriate treatment and poor outcomes. This report describes two patients with tuberculosis-associated HLH and reviews 55 other local and international cases reported in the literature.

Case reports

Case 1

A 78-year-old Chinese woman was admitted to hospital with a 1-week history of severe anorexia, fever, and left hip pain. Three months earlier, she had sustained a left intertrochanteric fracture after a non-syncopal fall, for which she had a dynamic hip screw insertion. She did not smoke or drink, and had well-controlled hypertension whilst taking amlodipine 5 mg daily. She had no personal or contact history of tuberculosis. Physical examination revealed that she was cachexic and dehydrated, with a temperature of 36.5°C, blood pressure of 165/98 mm Hg, heart rate of 91 beats/min, and a body weight of 53 kg. Muscle power was reduced to grade 4/5 in the left lower limb and left hip movement was limited by pain. The healed wound over the left hip looked unremarkable.

After admission, the patient was noted to have persistent fever despite broad-spectrum antibiotic cover including β-lactams (sequential use of intravenous amoxicillin/clavulanate, ceftriaxone, ceftazidime and meropenem), oral azithromycin, and oral doxycycline. Significant blood test abnormalities included: pancytopaenia, hypoalbuminaemia, deranged liver function, hypertriglyceridaemia, hyperferritinaemia, raised lactate dehydrogenase, C-reactive protein level, and erythrocyte sedimentation rate levels. She had a coagulopathy that included hypofibrinogenaemia and a raised D-Dimer level (Table 1). Clotting factor assays suggested vitamin K deficiency, whilst tests for the lupus anticoagulant and anti-cardiolipin antibody were negative, as was the factor inhibitor screen. She underwent bone marrow aspiration and biopsy, which revealed increased reactivity of histiocytes showing haemophagocytic activity (Fig 1a). Given the constellation of fever, pancytopaenia, hypertriglyceridaemia, hyperferritinaemia, hypofibrinogenaemia, and haemophagocytosis in bone marrow, a diagnosis of HLH was established.

She underwent extensive workup to elucidate the underlying cause of the HLH. The tumour markers and autoimmune markers were normal, making the possibility of malignancy and autoimmune disease unlikely. Serial chest radiographs showed gradual deterioration with the appearance of miliary shadows suggesting infection, particularly tuberculosis as the primary abnormality. Empirical anti-tuberculous treatment (isoniazid, rifampicin, ethambutol and pyrazinamide) was commenced. Subsequently, gallium scan showed intense focal uptake at the left sub-trochanteric region, mild left chest infection, and right hilar lymphadenopathy. Contrast computed tomography of the brain, thorax, abdomen, pelvis, and the left hip revealed the presence of diffuse miliary nodules in both lung fields (Fig 1b). There was a small abscess measuring 1.2 cm in diameter in the right psoas muscle and another measuring 4.7 cm x 3.9 cm x 8 cm over the lateral side of the

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噬血症候群：一種罕見肺結核病的臨床表現

繼發性噬血症候群是一種罕見但可致命的肺結核病的併發症。本文報告兩個有關病例，並討論本地及外國對於這種病的治療方法。及時使用抗結核藥物是成功治療噬血症候群的基石。

TABLE 1. Blood test abnormalities of cases 1 and 2

Blood test	Level		Reference range
	Case 1	Case 2	
Total white cell count (x 10^9 /L)	1.70	1.77	4.4-10.10
Haemoglobin (g/L)	86	88	124-168
Platelet count (x 10^9 /L)	37	29	170-380
Albumin (g/L)	15	18	39-50
Alkaline phosphatase (U/L)	321	190	42-110
γ-Glutamyltransferase (U/L)	216	-	11-62
Aspartate aminotransferase (U/L)	131	-	15-38
Triglyceride (mmol/L)	2.8	-	<1.7
Ferritin (pmol/L)	>33 000	1530	52-738
Lactate dehydrogenase (U/L)	751	291	118-221
C-reactive protein (nmol/L)	1057	706	<72.4
Erythrocyte sedimentation rate (mm/h)	96	-	0-20
International normalised ratio	2.0	1.3	-
Activated partial thromboplastin time (s)	58	50	25.9-33.7
Thrombin time (s)	37	-	11-15
Fibrinogen (μmol/L)	1.18	3.38	4.29-9.94
D-Dimer level (nmol/L)	11-44	3-11	<3

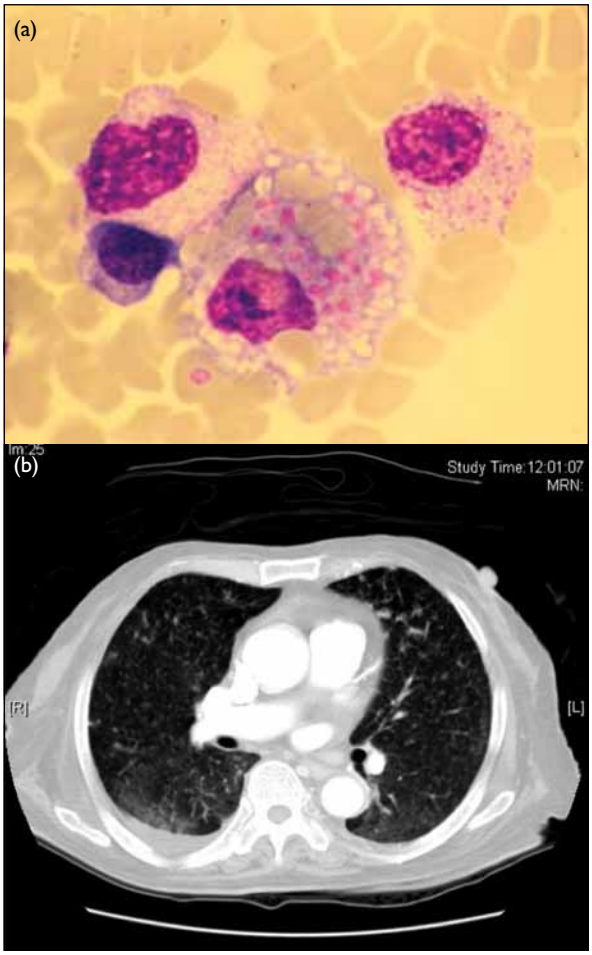

FIG 1. Case 1: (a) Bone marrow smear showing ingestion of erythrocytes and platelets by activated macrophages (Wright Giemsa stain, x 100 oil immersion). (b) High-resolution computed tomography of the lungs showing numerous tiny nodules distributed diffusely in both lungs with a small right-sided pleural effusion and basal atelectasis

left hip. Ultrasound-guided drainage of the abscess yielded a few millilitres of blood-stained fluid. Gram stain of the smear as well as aerobic and anaerobic culture of the fluid were negative, as were tests for MTB by polymerase chain reaction (PCR), smear and culture for acid-fast bacilli (AFB). A lytic lesion in the left side of the fifth lumbar vertebrae was noted. Subsequently, culture of the blood, sputum, early morning urine, and bronchoalveolar lavage all yielded MTB, although the initial smears were all negative. The overall diagnosis was HLH secondary to disseminated tuberculosis. The patient's clinical status, biochemical parameters, and radiological abnormalities gradually improved after commencement of anti-tuberculous treatment, which was continued for 18 months. She remained well at follow-up 5 months after completion of the treatment.

Case 2

An 80-year-old Chinese man presented with severe anorexia and fever for 3 months. He was a chronic smoker, had a history of paroxysmal atrial fibrillation, and was taking aspirin. He had no personal or contact history of tuberculosis. On physical examination, the patient was cachexic and dehydrated. He had a blood pressure of 93/62 mm Hg, pulse rate of 63 beats/min, and temperature of 35.9°C. Left cervical lymphadenopathy was detected. Significant blood test abnormalities included pancytopaenia, hypoalbuminaemia, elevated levels of alkaline phosphatase, ferritin, lactate dehydrogenase and C-reactive protein. He had a coagulopathy with a prolonged activated partial thromboplastin time, as well as borderline fibrinogen, and raised D-Dimer levels (Table 1). His bone marrow aspirate revealed markedly increased reactive histiocytes and prominent haemophagocytic figures. His trephine biopsy showed prominent granulomatous inflammation comprising epithelioid histiocytes and Langhans

giant cells, and Ziehl-Neelsen staining showed many AFB. Given the constellation of fever, pancytopaenia, hyperferritinaemia, borderline fibrinogen and haemophagocytosis in bone marrow, a diagnosis of tuberculosis-related HLH was entertained.

Further workup included tests for tumour autoimmune markers, vitamin B12, folate, thyroid stimulating hormone, cortisol, and serum and urine protein electrophoresis, all of which yielded no abnormality. Chest X-ray did not show any consolidation. Positron emission tomography and computed tomography showed multiple segments of large bowel with thickening and hypermetabolism, mostly affecting the ascending colon (Fig 2). In addition, there were multiple hypermetabolic lymph nodes in the cervical region and mediastinum, and bilateral pleural effusions with partial collapse of both lower lobes. Early morning gastric aspirate and urine culture yielded MTB. Despite treatment with supportive blood product transfusion, and anti-tuberculous therapy comprising isoniazid, rifampicin, ethambutol and pyrazinamide, the patient's condition deteriorated progressively and he succumbed 1 month later.

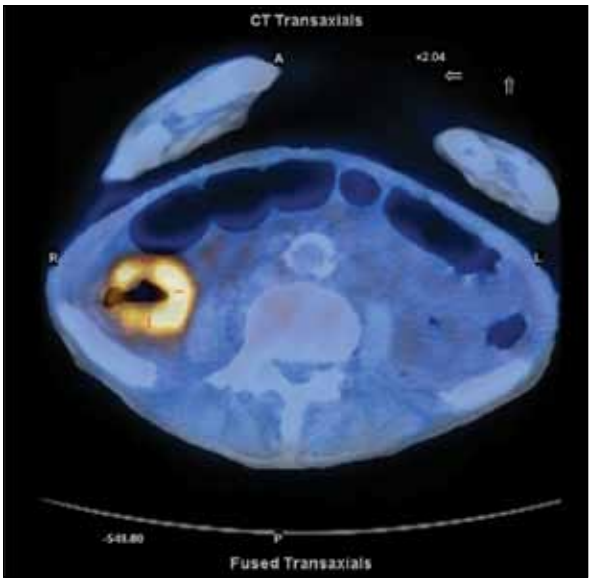

FIG 2. Positron emission tomography scan showing hypermetabolism and wall thickening at the ascending colon in case 2

Literature review

On 6 October 2011, we searched PubMed using the terms "tuberculosis", "hemophagocytic", "hemophagocytosis", and "lymphohistiocytosis". A total of 55 cases, three local (Table 2[3-5]) and 52 international (Table 3[6-47]), of tuberculosis-associated HLH were found.

Local cases

Including our patients, there were five locally reported cases of tuberculosis-associated HLH. Their mean age was 61 (range, 36 to 80) years; three were female and two male (Table 2). The most common clinical features were fever (80%), and pancytopaenia (80%) or bicytopaenia (in the remaining 20%). One of these five patients had splenomegaly, three had pre-existing conditions (nasopharyngeal carcinoma, sarcoidosis, and systemic lupus erythematosus) for which they received corticosteroids. Four of these patients received anti-tuberculous treatment, three of whom died (our case 1 being the exception), which gives an overall mortality of 80%.

International cases

The clinical details were available for 48 of the 55 reported cases (Table 3). Of the 45 patients in which the gender was reported, their mean age was 47 years (range, 14 days to 83 years), and 26 (58%) were male

TABLE 2. Local cases of tuberculosis-associated haemophagocytic lymphohistiocytosis

Patient No. [reference]	Gender/ age (years)	Site(s) of isolation of *Mycobacterium tuberculosis*	Co-morbidities	Fever	Hepatomegaly / splenomegaly	Platelet count (x 10^9 /L)	Immuno-therapy (form of therapy)	Anti-tuberculous treatment	Outcome
1 [3]	F/69	Lungs, cervical lymph nodes	Nasophageal carcinoma	Yes	No	70	No	No	Death
2 [4]	M/42	Lungs, kidneys, liver, spleen, prostate	Sarcoidosis	Yes	Splenomegaly	96	Yes (steroids)	Yes	Death
3 [5]	F/36	Blood, bone marrow	Systemic lupus erythematosus	Yes	No	92	Yes (steroids)	Yes	Death
4 (case 1)	F/78	Lung, L5 vertebrae, left greater trochanter collection, peripheral blood	Hypertension	Yes	No	37	No	Yes	Recovery
5 (case 2)	M/80	Lung, lymph node, bowel, urinary system, bone marrow	Paroxysmal atrial fibrillation	No	No	29	No	Yes	Death

TABLE 3. International cases of tuberculosis-associated haemophagocytic lymphohistiocytosis (HLH)*

Patient No. [reference]	Gender/ age (years)	Site(s) of isolation of *Mycobacterium tuberculosis*	Co-morbidities	Fever	Hepato-megaly / splenomegaly	Platelet count (x 10^9 /L)	Immunotherapy (form of therapy)	Anti-tuberculous treatment	Outcome
6 [6]	M/50	Adrenal glands	N/A	Yes	Yes	142	Yes (steroid)	Yes	Death
7 [7]	M/70	Liver, spleen, kidney, bone marrow, nodes from azygo-esophageal angle	N/A	Yes	Yes	130	Yes†	Yes	Death
8 [8]	M/43	Hilar lymph nodes, liver, bone marrow	N/A	Yes	Splenomegaly	157	Yes†	Yes	Recovery
9 [9]	M/76	Liver, spleen, lymphadenopathy, pancreas, kidneys, lungs, adrenal glands, vertebra	Small cell carcinoma	Yes	Hepatomegaly	Low	No	No	Death
10 [9]	F/68	Liver, spleen, lymph nodes, pancreas, lungs, kidneys, adrenal glands, endometrium, myometrium, large bowel	N/A	Yes	No	64	No	No	Death
11 [9]	M/59	Liver, spleen, lymphadenopathy, pancreas, lungs, kidneys, adrenal glands, mediastinal lymph nodes	Diabetes mellitus	Yes	No	Normal	No	No	Death
12 [10]	F/14	Lungs, bone marrow	N/A	Yes	Yes	113	Yes (epipodophyllotoxin)	Yes	Recovery
13 [11]	M/83	Lymph nodes, sputum, urine	N/A	Yes	No	120	No	Yes	Recovery
14 [11]	M/70	Mediastinal lymph nodes, spleen	N/A	Yes	No	37	Yes†	Yes	Recovery
15 [12]	M/38	Lungs, bone marrow	N/A	Yes	Yes	20	Yes (splenectomy)	Yes	Recovery
16 [13]	M/37	Bone marrow	Renal transplant on haemodialysis	Yes	Yes	15	No	No	Death
17 [14]	M/43	Lungs	AIDS	Yes	No	19	No	Yes	Death
18 [15]	M/40	Cervical lymph node	N/A	Yes	Yes	55	No	Yes	Recovery
19 [16]	F/73	Bone marrow	End-stage renal disease on haemodialysis	Yes	Yes	146	No	Yes	Recovery
20 [17]	M/22	Lymph nodes (HLH developed after anti-TB Rx)	N/A	Yes	Yes	10	No	Yes	Recovery
21 [18]	F/53	Blood	AIDS	Yes	Hepatomegaly	163	Yes (methyl-prednisolone, IVIG, and lenograstim)	Yes	Death
22 [19]	F/14 days	Blood, gastric, lungs	N/A	Yes	Yes	58	Yes (hydrocortisone)	Yes	Recovery
23 [20]	F/56	Lungs	Myelodysplastic syndrome, chronic glomerulonephritis on haemodialysis	Yes	Yes	45	Yes (steroid and plasma exchange)	Yes	Recovery
24 [21]	F/31	Lungs, bone marrow, cervical lymph nodes	Stage IV high-grade Hodgkin's lymphoma	Yes	Splenomegaly	Low	Yes (fludarabine, chlorambucil, and prednisone)	Yes	Recovery
25 [22]	M/40	Lungs	Renal dysfunction on haemodialysis	Yes	No	81	Yes (steroid and plasma exchange)	Yes	Recovery
26 [23]	F/9	Lungs, bone marrow, liver, spleen, central nervous system	N/A	Yes	Yes	47	Yes (prednisone)	Yes	Recovery
27 [24]	M/67	Liver, spleen, lungs, celiac lymph nodes, granuloma	Claudication; status post aorta-iliac bypass	Yes	Yes	150	No	No	Death
28 [25]	N/A / 44	N/A	Renal transplant, nephroangiosclerosis, haemodialysis	Yes	Yes	8	Yes (steroid and antithymocyte globulins)	Yes	Death
29 [25]	N/A / 45	N/A	B lymphoma, membranous nephropathy, renal transplant, haemodialysis	Yes	Yes	129	No	Yes	Recovery

TABLE 3. (Cont'd)

Patient No. [reference]	Gender/ age (years)	Site(s) of isolation of *Mycobacterium tuberculosis*	Co-morbidities	Fever	Hepato-megaly / splenomegaly	Platelet count (x 10^9 /L)	Immunotherapy (form of therapy)	Anti-tuberculous treatment	Outcome
30 [26]	F/7 weeks	Lungs	N/A	Yes	Yes	125	No	No	Death
31 [27]	F/60	Lungs	N/A	Yes	Hepatomegaly	-	No	Yes	Recovery
32 [28]	M/75	Lungs, bone marrow	Chronic renal failure on haemodialysis	Yes	No	121	Yes (IVIG)	Yes	Death
33 [29]	F/29	Lung	N/A	Yes	Yes	437	No	Yes	Recovery
34 [30]	F/83	Bone marrow	Chronic renal failure on haemodialysis, hypertension	Yes	Splenomegaly	37	No	No	Death
35 [31]	M/52	Lungs	N/A	Yes	No	268	No	Yes	Recovery
36 [32]	M/40	Lungs, stomach	Candidial oesophagitis	Yes	Yes	30	Yes (methyl-prednisolone, and IVIG)	Yes	Recovery
37 [32]	M/46	Ileum	N/A	Yes	Yes	303	No	Yes	Recovery
38 [33]	M/15	Bone marrow, liver, spleen, lymph nodes	N/A	Yes	Hepatomegaly	65	Yes (IVIG)	Yes	Recovery
39 [34]	M/28	Liver, small bowel, colon	Schistosomiasis	Yes	Splenomegaly	118	Yes (dexamethasone)	Yes	Death
40 [35]	M/63	Lung, bone marrow	Diabetes mellitus	Yes	Yes	78	Yes (etoposide)	Yes	Death
41 [36]	M/41	Mediastinal and hilar lymph nodes	Wegener's granulomatosis (received 3 infusions of infliximab for scleritis and uveitis)	Yes	Yes	196	Yes (vincristine)	Yes	Recovery
42 [37]	M/17	Lymph nodes, bone marrow	N/A	Yes	Yes	70	Yes (dexamethasone)	Yes	Recovery
43 [38]	N/A / 30	Lungs, pleura, mediastinal lymph nodes	N/A	Yes	N/A	Low	Yes (steroid)	Yes	Recovery
44 [39]	M/52 days	Lungs, liver, lymph nodes	Seborrhoeic dermatitis	Yes	Yes	75	Yes (IVIG)	Yes	Death
45 [40]	F/48	Lungs, bone marrow	Crohn's disease (received infliximab)	Yes	Yes	Low	Yes (steroid and IVIG)	Yes	Recovery
46 [41]	F/70	Multiple organs	Acute renal failure due to crescentic glomerulonephritis on haemodialysis	Yes	N/A	Low	Yes (chemotherapy, and steroid)	Yes	Death
47 [42]	M/68	Bone marrow	N/A	Yes	Yes	25	Yes (prednisolone)	Yes	Recovery
48 [42]	F/67	Lungs, bone marrow	N/A	Yes	No	114	Yes (methyl-prednisolone)	Yes	Death
49 [43]	F/76	Lungs, bone marrow	N/A	Yes	No	Low	Yes (steroid)	Yes	Recovery
50 [44]	F/59	Lungs	N/A	Yes	N/A	Low	Yes (steroid)	Yes	Death
51 [45]	M/48	Lungs, urine, bone marrow	N/A	Yes	N/A	Low	Yes (methylprednisolone, etoposide)	Yes	Recovery
52 [46]	F/63	Bone marrow, lungs, liver, spleen, kidney	Aplastic anaemia	Yes	N/A	Low	Yes (methyl-prednisolone)	No	Death
53 [47]	F/56	Bone marrow	Diabetes mellitus complicated with nephropathy	Yes	N/A	Low	No	No	Death

* AIDS denotes acquired immunodeficiency syndrome, anti-TB Rx anti-tuberculous treatment, IVIG intravenous immunoglobulin, and N/A not available

† Form of immunotherapy was not described

and 19 (42%) were female. Among them, 42% had underlying co-morbidities; eight had chronic renal failure, four had malignancy, three had diabetes mellitus, two had acquired immunodeficiency syndrome (AIDS), two were in receipt of infliximab for Crohn's disease and Wegener's granulomatosis, and one had aplastic anaemia. All 48 patients had fever, and 47 (98%) had thrombocytopaenia. Of the 42 cases in which the presence or absence of hepatosplenomegaly was reported, 32 (76%) had such organomegaly. Overall mortality in these 48 patients was 44%. All nine patients who did not receive anti-tuberculous treatment died. Among patients who received anti-tuberculous treatment with or without immunotherapy, the survival rate was 68% (27/40), the highest rate (9/10) being in those who did not receive immunotherapy. The immunotherapies reported to have been given included high-dose steroids, intravenous immunoglobulin, chemotherapy (eg etoposide or vincristine), splenectomy, plasma exchange, and epipodophyllotoxin.

Discussion

Being a disorder of the macrophage lineage, HLH is characterised by the finding of haemophagocytosis (ie activated macrophages engulfing erythrocytes, leukocytes, platelets, and their precursor cells). The disorder is classified into primary and secondary forms. Primary or familial HLH belongs to a group of genetic diseases with impaired immune cell function (cytotoxic T and natural killer [NK] cells) that affects children, usually before the age of 2 years. Secondary HLH may occur at any age and is usually caused by infections, autoimmune diseases, malignancies, or drugs[2,42] (Table 4). The diagnosis of HLH is deemed to be made when at least five of the following eight criteria are fulfilled[2]:

(a) Splenomegaly
(b) Fever (>7 days)
(c) Bicytopaenia without marrow hypoplasia including haemoglobin <90 g/L, platelet count <100 x 10^9 /L, neutrophil count <1.10 x 10^9 /L
(d) Fasting hypertriglyceridaemia (>3.0 mmol/L) and/or hypofibrinogenaemia (<1.5 g/L)
(e) Hyperferritinaemia (>500 μg/L; 1125 pmol/L)
(f) Low or absent NK cell activity
(g) Increased soluble CD25 levels (>2400 IU/mL)
(h) Histologically evident haemophagocytosis

Tuberculosis is an uncommon but important cause of secondary HLH, accounting for about 3% of all cases, and affects all age-groups.[2] Failure to establish the diagnosis of HLH secondary to tuberculosis inevitably leads to an adverse outcome. While patients may have clinically overt symptoms and signs suggestive of tuberculosis, occasionally the manifestations may be subtle or atypical. Among the local cases, 4/5 (80%) did not have any respiratory symptom in the initial stage (patients 1, 3, 4, and 5). Furthermore, unlike the international cases, hepatosplenomegaly was rare (20% vs 76%). As tuberculosis is endemic in our region, this treatable cause should be actively sought in all our patients with HLH. This entails collecting specimens, including sputum, early morning gastric aspirates, early morning urine, peripheral blood, and even body tissues (eg bone marrow and lymph node aspirates) for PCR, as well as microscopy and culture for AFB. Although mycobacteraemia is rare (8%) in human immunodeficiency virus (HIV)–negative patients with active tuberculosis, blood cultures for mycobacteria should be performed in clinically suspicious cases, as they may provide the first clue to underlying tuberculosis, as in patients 3 and 4 who had a peripheral blood smear positive for AFB and a blood culture positive for MTB, respectively. There were also two more patients with positive blood cultures for MTB among the international cases.[18] Culture of the bone marrow appears to be a more sensitive test than peripheral blood cultures (38% vs 8%) to make the diagnosis.[48] Prior to obtaining blood cultures for AFB, the microbiology laboratory should be alerted

TABLE. 4 Aetiologies of secondary haemophagocytic lymphohistiocytosis (adopted from Claessens et al[42])

Infection*	Immune disorders	Drugs	Neoplasms	Inflammatory diseases
Virus: herpes virus group, parvovirus B19, myxovirus, para-influenza virus, HIV, hepatitis, enterovirus, morbillivirus	Duncan's disease (Purtilo syndrome), Chédiak-Higashi syndrome, asplenia, cytotoxic drugs	Phenytoin, carbamazepine, minocycline, phenobarbital	Malignant lymphoma (especially T cell lymphoma, angioimmunoblastic lymphadenopathy)	Systemic lupus erythematosus, Still's disease, rheumatoid arthritis, scleroderma, sarcoidosis, Kikuchi syndrome, Crohn's disease, histiocytic cytophagic panniculitis
Bacteria: *Brucella*, mycobacteria, salmonella, mycoplasma, ehrlichia, rickettsia, borrelia, common bacteria			Hodgkin's lymphoma, tricholeukocyte leukaemia, myelodysplastic syndrome, solid neoplasm	
Parasites: anguillulose babesia, leishmania, plasmodium, toxoplasma				
Fungus: candida, histoplasma, aspergillus, cryptococcus				

* HIV denotes human immunodeficiency virus

of the possibility, in order to use selective broths and culture methods to enhance the diagnostic yield.

Though the exact pathogenesis of tuberculosis-associated HLH is not clearly known, it is likely the phenomenon is related to immune dysregulation. Tuberculosis normally induces a Th1 response, in which cytotoxic Th1 cells and macrophages cooperate to increase the efficiency of cytotoxic lymphocytes and the capacity of macrophages to proliferate.[2] In secondary HLH, defective cytotoxic T cells and NK cells produce a disordered and inadequately regulated immune response that may result in the survival and proliferation of bacteria with ongoing immunological stimulation. Furthermore, the NK cells may be unable to regulate the immune response by effectively destroying the proliferating immune cells. The result could be a cytokine storm with uncontrolled macrophage proliferation manifesting as a variety of clinical and laboratory abnormalities.[34] Fever and tissue wasting are mainly caused by tumour necrosis factor-α (TNF-α).[6] Cytopaenia results from haemophagocytosis in the bone marrow and depression of haematopoiesis by inhibitory cytokines such as interferon-γ (IFN-γ), TNF-α and interleukin-1β (IL-1β). Haemolysis leads to hyperbilirubinaemia and elevation of lactate dehydrogenase. Serum ferritin elevation is due to IL-1β elevation.

Hypertriglyceridaemia is due to lipoprotein lipase inhibition by TNF-α, whilst IFN-γ contributes to the development of cholestasis. Colony-stimulating factor together with Fas/Fas-ligand interaction in response to IFN-γ overproduction may contribute to apoptosis and liver damage. Elevation of IFN-γ levels leads to hypoalbuminaemia. Renal failure results from abnormally high concentrations of nephrotoxic IL-6. Other non-specific but possible laboratory abnormalities include hypo- or hyper-gammaglobulinaemia, a positive Coomb's test, and hyponatremia due to the syndrome of inappropriate anti-diuretic hormone secretion.[2] Coagulopathy may be related to thrombocytopaenia, hypofibrinogenaemia, or disseminated intravascular coagulation.[2] Hypofibrinogenaemia is caused by activated macrophages, which can activate factor X of the coagulation cascade through Mac-1 receptors and activate the common pathway.[49] Ooe[49] also demonstrated that in autopsies of patients with familial HLH, fibrinogen antigens could be detected in the cytoplasm of approximately 10% of splenic histiocytes showing a diffuse staining pattern, indicating uptake of fibrin and/or fibrinogen molecules by these cells.

There is a risk of developing tuberculosis-associated HLH in the elderly population, in whom immunosenescence may be an important contributing factor. There were 16 cases of tuberculosis-associated HLH reported in patients aged >65 years; eight were male and eight were female, and six (38%) had underlying comorbidities (2 had malignancies and 4 had underlying renal impairment). Immunosenescence is a multifactorial condition and consists of various age-related changes, including thymic involution, reduction of naïve T cells, decreased antigen responsiveness and proliferation.[50,51] The NK cells are also less readily activated by IFN-α and have reduced cytotoxic activity, possibly by an intracellular decrease in calcium mobilisation.[51] The increased production of prostaglandin E_2 by aged activated macrophages may decrease T cell activation.[51] Aged macrophages also generate reduced amounts of nitric oxide and superoxide and have diminished Toll-like receptor expression and function.[51]

Tuberculosis-associated HLH confers a high overall mortality (80% among local cases, and 44% among international cases), which was mainly due to under-recognition of the condition and delayed institution of treatment. As evident in our case 1, negative smear results in early investigations did not exclude the diagnosis. Empirical anti-tuberculous treatment should be considered if there is a high degree of clinical suspicion, such as persistent fever despite broad-spectrum antibiotic treatment, and interval radiological deterioration. First-line anti-tuberculous drugs, including isoniazid, rifampicin, pyrazinamide, and ethambutol, can be appropriate. We were only able to trace the duration of treatment in two of the 27 successfully treated cases; one received 9 months of therapy[31] and the other 12 months.[19] The World Health Organization guideline recommends treatment durations beyond 6 months in disseminated or extrapulmonary infections. The exact duration should be decided on a case-by-case basis.[52]

Besides anti-tuberculous medications, other therapeutic options may serve as useful adjuncts in tuberculosis-associated HLH. They include various immunotherapies, among which glucocorticoids are the most common. The aim of steroid therapy is to control the intense inflammatory reaction and cytokine storm, so as to improve clinical outcomes. In most cases however, details of the dosage and duration of therapy were not reported. Overall survival rates in those who received such adjunctive steroid therapy and those who did not were 57% (12/21) and 83% (10/12), respectively. However, given the limited number of case reports, and the differences in the choice, dosage and duration of steroid therapy, recommendations cannot be made based on the available comparisons. Further controlled studies appear necessary before making a recommendation on their optimal use, if any. Other immunotherapies (intravenous immunoglobulin, chemotherapy with etoposide or vincristine, splenectomy, plasma exchange, and epipodophyllotoxin) have also met with variable success. As the number of patients with tuberculosis-associated HLH was limited, the role of such immunotherapeutic agents remains unclear.

Another important adjunctive therapy is highly active anti-retroviral therapy (HAART), which should be started within the first 8 weeks of anti-tuberculous treatment in patients having underlying HIV infection. After the commencement of HAART, the occasional patient may experience paradoxical clinical deterioration due to the immune reconstitution syndrome. Although this was not encountered in the patients listed in this series, clinicians should be aware of the possibility and adjust the treatment accordingly on a case-by-case basis. Finally, as in our first patient who had a psoas muscle and hip abscesses, infected collections might warrant surgical or image-guided drainage to augment diagnostic and therapeutic success.

Conclusions

In the presence of active tuberculosis, HLH is rare but serious. In HLH patients, physicians should have a high degree of clinical vigilance and actively seek out tuberculosis by means of relevant investigations. Early use of appropriate anti-tuberculous treatment is important in preventing unnecessary morbidity and mortality.

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