Case Report

Infections associated with haemophagocytic syndrome A case report of a rare coexistence with common infections

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Abstract

Infection-associated haemophagocytic syndrome (IAHS) is exceptional in typhoid and tuberculosis co-infections. We encountered a 50-year-old man with a history of pacemaker implantation who was previously treated for typhoid fever and currently presented with a chronic fever and shortness of breath. Initial laboratory tests revealed pancytopenia. A bone marrow aspiration was performed. However, due to cardiac problems, a bone marrow biopsy could not be performed. A bone marrow aspirate was submitted for cell block preparation. The cytology of the bone marrow aspirate revealed hemophagocytosis, which was initially presumed to be secondary to typhoid. Subsequently, cell block preparation of the bone marrow aspirate exhibited numerous granulomas with necrosis suggestive of tuberculosis. The patient was successfully treated with anti-tuberculosis drugs, steroids, and antibiotics. This case highlighted an association between IAHS and a common tropical illness. The usefulness of an aspirate cell block in the absence of biopsy and the potential existence of tuberculosis, especially in tuberculosis-endemic countries is to be noted.

Keywords: *Infection-associated haemophagocytic syndrome, Typhoid, Tuberculosis, Bone marrow aspirate*

Introduction

Haemophagocytic syndrome or haemophagocytic lymphohistiocytosis (HLH) is defined by a relentless activation of CD8+ T cells and macrophages which cause organ damage, especially in the liver, bone marrow, and central nervous system. Clinical and biochemical symptoms of HLH include fever, splenomegaly, pancytopaenia, hypertriglyceridaemia, and hyperferritinaemia.[1] HLH comes in two distinct forms: Primary HLH (inherited) occurs in children with genetic immunodeficiency, whereas

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secondary HLH (acquired) occurs in the presence of infections, autoimmune disorders, or cancer. Infection-associated HLH (I-HLH) is most common in viral infections and less common in bacterial, fungal, and parasitic disorders.[2] The coexistence of typhoid and tuberculosis that results in I-HLH and a diagnosis of tuberculosis using bone marrow aspirate cell block preparation has not been previously described.

Case Report

A 50-year-old male patient arrived at our hospital's emergency room with a three-week history of fever, shortness of breath and a cough for three days. The patient was admitted initially to a private nursing home, where he was diagnosed with typhoid fever based on a Widal test and treated with parenteral ceftriaxone and oral ofloxacin. In spite of the initial treatment, fever spikes continued and because of new-onset shortness of breath, the patient was referred to our hospital. The details of the previous blood culture and Widal reports were not provided. He had a pacemaker implanted a year ago for a third-degree heart block. The patient was pale and febrile (38.2 °C) and with tachycardia of 110 beats/minute, blood pressure of 100/60 mmHg, and a respiratory rate of 32 breaths/ minute. There were no signs of inflammation
around the pace maker implant, lymphadenopathy, jaundice, or cyanosis. Systemic examination was unremarkable except for crackles with limited air entry at the base of the lungs.

Preliminary laboratory testing revealed pancytopenia (Table 1). A peripheral blood smear showed normocytic normochromic RBCs and neutrophil predominance (81%). The reticulocyte count was 0.5% and the erythrocyte sedimentation rate (ESR) was high (70 mm at the end of one hour). The results of the blood coagulation tests showed a slight rise in prothrombin time (PT), but no change in activated partial thromboplastin time (APTT) or fibrinogen. The procalcitonin level (0.4 ng/ml) was normal. The level of an N-terminal pro-b-type natriuretic peptide (NT-proBNP) was markedly elevated at 20236 pg/ml (normal: 0-125 pg/ml). Serological tests for HBV, HCV, HIV, and syphilis were negative. Biochemical tests revealed indirect bilirubinaemia, hypoalbuminaemia, hyponatraemia, hypokalaemia and normal serum creatinine (Table 1).

The malarial parasite, malarial antigen, dengue serology and leptospira tests were all negative. Typhoid IgG/IgM (CTK Biotech Rapid test cassette) was found to be positive by lateral flow immunochromatography.

Radiological imaging X-ray chest (anteroposterior view) showed the pacemaker in situ. Non-homogenous opacity with patchy consolidation in bilateral lung fields suggestive of pulmonary edema was noted. The right costo-phrenic angles were indistinct with minimal pleural effusion. An ultrasound of the abdomen showed liver congestion with mild splenomegaly (135 mm) and mild ascites. The 2-D echocardiography revealed a 30% left ventricle ejection fraction, severe left ventricular dysfunction, and a dilated ventricular chamber. He was put on NIV (non-invasive ventilator) support and a diuretic (furosemide) infusion was initiated. Hypokalemia was corrected and he was transferred to the critical care unit.

Table 1: Laboratory data

Laboratory Investigations	Test Results					Biological reference interval
	Day 1	Day 2	Day 5	Day 10	Day 14	
Haemoglobin	100	98	100	101	103	120-150 g/L
WBC	2.4	2.5	3.4	3.90	4.2	4.0-11x10^9/L
Platelets	145	140	148	160	175	150-450x10^9/L
ESR	70				42	0-15 mm of 1 hr
Total Bilirubin	1.8		1.3		1.2	0.2 - 1.3 mg/dL
Direct	0.2		0.2		0.1	0 - 0.3 mg/dL
Indirect	1.6		1.1		1.1	0 - 1 mg/dL
SGOT	57		98		41	14 -60 U/L
SGPT	46		32		26	0 -35 U/L
Alkaline Phosphate	124		158		111	38-126 U/L
Total Protein	5.8		6.4		6.2	6.3 - 8.5 gms/dL
Albumin	2.7		2.8		2.8	3.5 - 5.0 gms/dL
Globulin	3.1		3.5		3.4	2.3 - 3.5 gms/dL
SLDH		916	879	616	384	120 - 246 U/L
S. Creatinine	60		70		90	70- 120 µmol/L
S. Ferritin		1380	1110		607	13 - 150 ng/ml
Sodium	140	144	150	148	150	13.7-145 mmol/L
Potassium	3.0	3.4	3.6	3.8	3.8	3.5-5.1 mmol/L
Prothrombin Time	16.6		13.8		13.7	12.3 - 15.2 sec
INR	1.28		1.0		0.99	<1.3 sec
APTT	30		29.1		29.5	26.2-32.1 sec
Serum Fibrinogen	--	58	68		180	200 -400 mg/dL
Serum Triglicyrides	--	320			185	<150 mg/dL

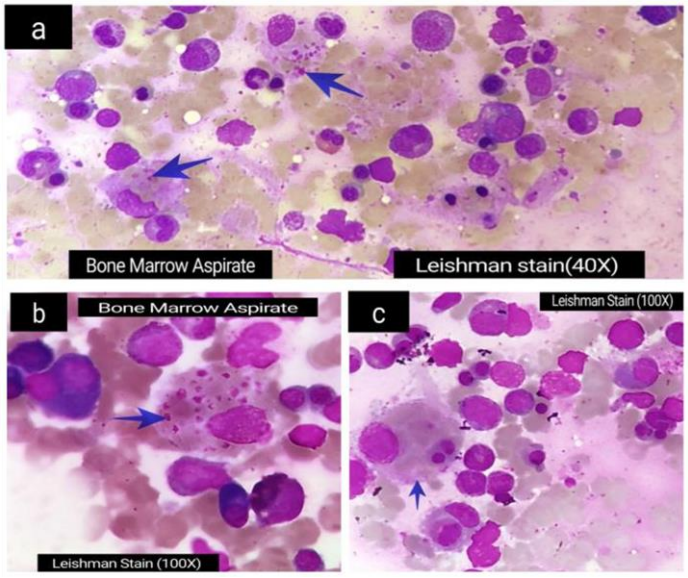

Figure 1: Bone marrow aspirate cytosmears (Leishman stain 40 X) showed haemophagocytes (blue arrow).

A bone marrow aspiration and biopsy were planned due to pancytopaenia. The aspirated bone marrow material was particulated. However, a bone marrow biopsy could not be performed because the patient had tachycardia and palpitations upon aspiration. A cytosmear showed many macrophages engulfing haematopoietic elements (haemophagocytes) in the cytology smears (Figure 1). Since there were no atypical cells, aspirated bone marrow was submitted for cell block preparation.

The diagnosis of haemophagocytic syndrome (HLH) was considered based on fever, pancytopenia, splenomegaly, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and evidence of haemophagocytes in the bone marrow (7 of 8 criteria according to the Histiocyte Society 2004 criteria).[9] However, subsequent bone marrow aspirate cell block sections revealed numerous granulomas composed of epithelioid cells, multinucleated Langhans giant cells and foci of necrosis (Figure 2). Ziehl-Neelsen (Z-N) staining was positive for acid-fast bacilli.

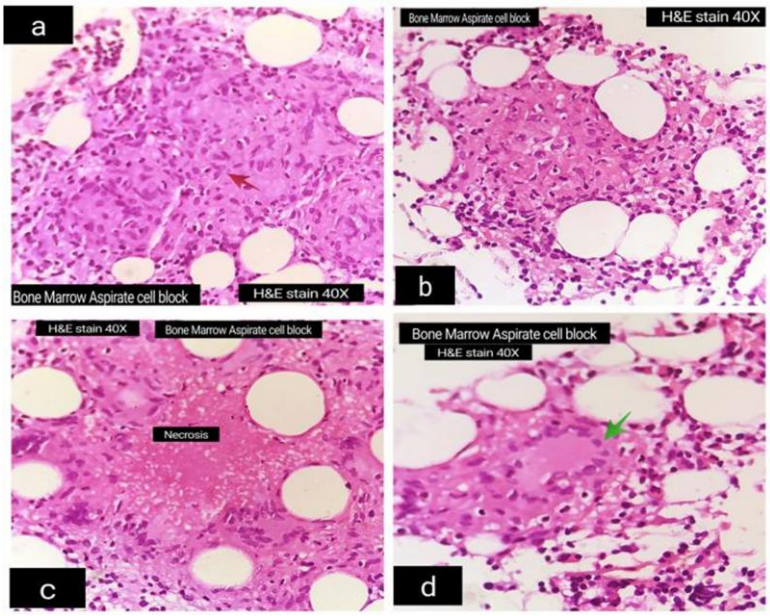

Figure 2: Bone marrow aspirate cell block section showed granuloma consisting epithelioid cells (red arrow) (Figure 2a and 2b). Caseation necrosis (Figure 2c) and Langhans giant cell (Figure 2d).

The patient was treated with intravenous methylprednisolone (1 mg/kg/day) for three days, followed by oral prednisolone in a gradually tapering dose and was initiated on antitubercular drug therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) with the continuation of antibiotics (ceftriaxone 1gm IV two times for seven days and oral ofloxacin 200 mg two times for five days), statins (atorvastatin 20mg/day) and diuretics (spironolactone 25mg /day). Serial monitoring of biochemical parameters was conducted (Table 1). The patient improved symptomatically and was discharged after two weeks in a stable condition.

The timeline of the patient's illness post-admission is presented below (Figure 3).

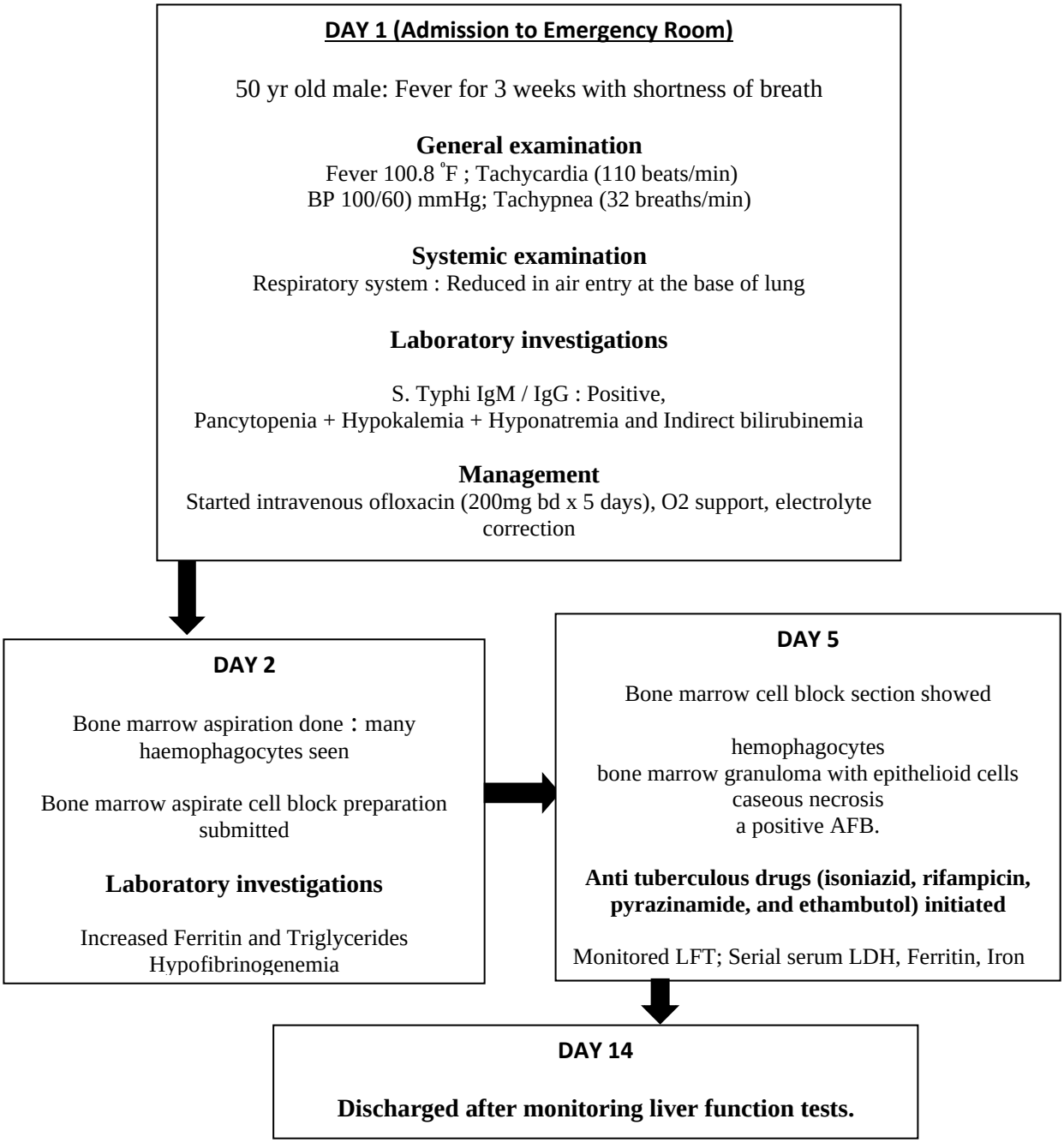

Figure 3: Time line of patients' illness post admission

Discussion

Typhoid and tuberculosis (TB) are caused by *Salmonella* Typhi and *Mycobacterium tuberculosis*, respectively. Although both are uncommon in developed nations, they are of substantial concern in developing countries. Due to clinical overlap with other febrile disorders and a lack of good diagnostic laboratory standards, establishing the precise burden in developing nations is difficult.[3] The presence of *Salmonella Typhi* isolates in blood or bone marrow aspirate (BM) cultures is the gold standard for diagnosing typhoid fever. Since bone marrow aspiration is an invasive and technically complex procedure, peripheral blood for serological and cultural diagnosis of typhoid takes priority over bone marrow aspiration for culture. Typhoid IgG/IgM is currently

identified by a lateral flow immunoassay for qualitative detection and screening, providing a preliminary result to aid in the diagnosis of *Salmonella* Typhi infection.[4] Mohamed et al. conducted a recent study in which blood samples were collected from 90 patients (of all ages) who had fever lasting more than four days. The Typhoid IgG/IgM combo test (lateral flow immunoassay) results were positive in approximately 24% of all patients and demonstrated 72.4% sensitivity, 98.4% specificity, 95.5% positive predictive value and 88.2% negative predictive value.[5]

Our patient started with a fever but without respiratory symptoms. As a patient with a pacemaker implant, he was thoroughly investigated for an infection. Except for the typhoid IgG and IgM, all other serological tests (brucella, leptospira and dengue) were negative. Pancytopenia with a history of fever that did not respond to initial treatment was addressed with an invasive bone marrow procedure.

A bone marrow aspirate cell block section aids in the diagnosis of tuberculosis without the need for a biopsy. As recommended by the International Council for Standardization in Haematology (ICSH), cell block preparation of the aspirated sample was examined as a trephine biopsy could not be performed in this patient.. The aspirated and sectioned clot was documented similarly to the BM trephine.[6]

Tuberculosis is the most common cause of granulomas identified in 0.3% to 3% of bone marrow biopsies. Basu et al. conducted a clinicopathological study of 14 bone marrow aspirate granulomas identified by a trephine biopsy. In 13 of the 14 instances, BM granulomas were found in biopsy, while epithelioid cells were seen in one BM aspirate.[7] Wang Yu et al. researched 110 cases of bone marrow granulomatous lesions in marrow biopsies where granulomas were observed in trephine biopsies and reported that tuberculosis was the most common cause of bone marrow granulomas.[8] Diagnosis of tuberculosis on bone marrow aspirate cell block preparation based on the presence of granulomas and positive acid-fast bacilli on Z-N staining, as found in our case, has not been reported in the literature.

HLH is a hyperinflammatory syndrome that results in immunological hyperactivation, hypercytokinaemia and uncontrolled haemophagocytosis. To diagnose HLH, five of the eight criteria established by the Histiocyte Society in 2004 must be met.[9] Our patient met seven criteria: fever, pancytopenia, splenomegaly, hyperferritinaemia, hypertriglyceridaemia, hypofibrinogenaemia andevidence of hemophagocytes in the bone marrow. Antimicrobials targeting suspected or confirmed pathogens, such as antivirals, antibiotics, or antifungal therapy with a combination of immunosuppressive and cytotoxic therapy to target the hyperinflammatory state were recommended for patients with I-HLH, regardless of the type of infectious agent.[2] In cases of remission, haematopoietic stem cell transplantation (HSCT) is the only curative treatment option. Prognosis varies according to the underlying cause but is nevertheless disappointing in adulthood with the mortality rate ranging from 41% to 79%.[10] Improving the outcome necessitates early diagnosis and treatment.

Conclusion:

The co-infection of typhoid with tuberculosis causing HLH and diagnosed by bone marrow aspirate cell block preparation has not been previously described. There were difficulties in establishing typhoid as a coinfection in this patient. However, the

association was strongly confirmed by positive serological testing. In cases of persistent fever with pancytopaenia, the possibility of I-HLH should be considered and bone marrow aspiration and biopsy should be performed for the presence of haemophagocytes, as well as bone marrow aspiration for culture to rule out coinfection, especially in countries where tuberculosis and typhoid are endemic.

Declaration

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Ethics statement: Consent for publication of case report was obtained from the patient. A written/ verbal consent was obtained from both patient and attendants
Authors' contributions: The data collection and laboratory processing of samples was by MM, RDS, and RH. The management of the patient was by KS. The manuscript was drafted by MM and was critically evaluated by AA. All authors read and reviewed the manuscript .

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