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Case report

Secondary hemophagocytic lymphohistiocytosis triggered by *Staphylococcus aureus* bacteremia: A case report and systemic review

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ABSTRACT

Adult haemophagocytic lymphohistiocytosis (HLH) is an infrequent and life-threatening condition. The most common triggers of HLH are malignancy and virus, and bacterial infections are rarely implicated. We present a case of HLH secondary to *Staphylococcus aureus* infection and systemically searched the PubMed database for publications on HLH associated with *Staphylococcus aureus* infection and reviewed nine cases from seven studies. A marked third of patients had infective endocarditis, while the mortality rate was 44 %. HLH developed in our case despite elimination of MRSA from the bloodstream, leading to eventual demise of our patient, suggesting that prolonged hyperimmune response may persist even after the elimination of initial triggering factor. Our case highlights the necessity of high clinical suspicion and prompt diagnosis of HLH.

Introduction

Adult haemophagocytic lymphohistiocytosis (HLH) is a rare and life-threatening condition, occurring in approximately 1.2 cases per 1000,000 individuals per year. It is an immune-mediated and life-threatening disease that is caused by impaired natural killer and cytotoxic T-cell function [1], classified as primary (genetic) and secondary (reactive) according to the cause of disease. Underlying genetic defects have significant influence on HLH, while nearly a third of reported cases in adults have more than one underlying cause. Trigger agents of secondary HLH include infection, neoplasms, autoimmune diseases, and even drugs. MRSA is a rare trigger agent in secondary HLH. We present an 86-year-old Taiwanese woman who was found to have *Staphylococcus aureus* bacteremia and pneumonia complicated with secondary HLH.

Case report

An 86-year-old Taiwanese woman with multiple comorbidities presented to the emergency department of a medical center with complaints of dizziness during a routine hemodialysis session caused by intradialysis hypotension. At triage, she had a body temperature of 35.9 °C, a heart rate of 101 beats per minute, a blood pressure of 111/64 mmHg, and a respiratory rate of 18 with saturations above 95 % on ambient air. No pale conjunctive or dry oral mucosa was noted, and her heart sound was regular without audible murmur. The rest of her exam was unremarkable.

The laboratory results are shown in Table 1. She was found to have marked leukocytosis and neutrophilia (93 % neutrophil) and an elevated procalcitonin and lactate. She was admitted to ordinary ward for suspecting catheter-related blood stream infection. Empirical antibiotics of ceftriaxone and teicoplanin were administered since then. Both the peripheral and the catheter blood cultures obtained in the emergency room

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Table 1
Laboratory values on admission.

	Patient lab values	Normal range
Hemoglobin, (g/dL)	11.5	11 −16
Platelets, ($\times 10^9$/L)	115	140 −450
White blood cell, ($\times 10^9$/L)	30.3	4.0 −10.0
Bicarbonate, (mmol/L)	33	20 −26
Potassium, (mmol/L)	3.4	3.5 −5.1
Sodium, (mmol/L)	137.0	136 −146
Blood urea nitrogen, (μmol/L)	7.5	2.86 −7.14
Creatinine (μmol/L)	344.76	35.36 −106.08
Aspartate Aminotransferase, (U/L)	33	15 −41
Lactate, (mmol/L)	3.51	0.5 −2.2
Procalcitonin, (ng/mL)	32.346	< 0.09

were positive for methicillin-resistant *Staphylococcus aureus* (MRSA) on day 2 of admission. She had been receiving hemodialysis through a Hickman catheter placed in the right internal jugular vein six months ago, and this was subsequently removed for concerns of catheter infection, while a temporary catheter was placed in the femoral vein for dialysis. Tip culture of the Hickman catheter showed presence of MRSA. Fever persisted and blood cultures were still positive for MRSA on day 5 and 10 of admission while chest radiograph showed new infiltrates suggestive of pneumonia. Antigen tests for influenza A and B and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) were negative. Antibiotic regimen was changed to linezolid for better penetration into the lungs as well as central nervous system. Due to persistent bacteremia, the temporary catheter for hemodialysis was changed. Subsequent blood cultures obtained on day 12, 15, and 20 showed no growth. Nevertheless, pneumonia progressed, necessitating endotracheal tube insertion, and septic shock developed, so she was transferred to intensive care unit (ICU) under critical condition on day 14 of admission. Transthoracic echocardiogram and transesophageal echocardiogram revealed no vegetation, but thrombi were found in the superior vena cava and right atrium. Technetium-99 m Methylene Diphosphonate (TC-99 m MDP) and Gallium-67 (Ga-67) scintigraphy revealed mild and diffuse inflammatory process in bilateral lungs. FilmArray Respiratory Panel (FilmArray RP) of the bronchoalveolar lavage (BAL) revealed *Staphylococcus aureus* (106 copies/microliter) along with presence of mecA, mecC, and MREJ (mecA recombinase locus homolog), indicative of MRSA. Polymerase chain reaction (PCR) of BAL were negative for Herpes Simplex Virus (HSV) and *Pneumocystis jirovecii*, while viral load of cytomegalovirus was 40.6 IU/mL only. PCR of blood did not detect Epstein-Barr Virus. Sputum cultures were negative for *Mycobacterium tuberculosis*. Sputum cultures and FilmArray RP were negative of Legionella pneumophila. Markers of hepatitis viruses A, B, C, and E, Human Immunodeficiency Virus (HIV), parvovirus B19, and human T-lymphotropic virus 1, were not checked. Computed tomography (CT) with dynamic injection of contrast medium of great vessel in chest revealed acinar consolidation in right upper lobe, left upper lobe, and right middle lobe without presence of lung abscess. Although thrombus in superior vena cava and right atrium was seen, there was no filling defect in pulmonary arteries (Fig. 1).

The patient developed refractory anemia without obvious blood loss or hemolysis, followed by marked leukopenia and thrombocytopenia on hospital day 18, which persisted despite usage of Granulocyte Colony-Stimulating Factor (G-CSF) and discontinuation of possible culprits such as linezolid and colchicine. Elevation of aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase, and ferritin were noted (Table 2). No splenomegaly was found on ultrasound. Bone marrow aspiration smear revealed histiocyte phagocyting erythrocytes (Fig. 2). Routine tests of soluble CD25 level and NK cell activity were not available in our hospital. There was no other suspected drugs other than linezolid and colchicine that could have caused bone marrow depression.

A diagnosis of MRSA infection with secondary hemophagocytic lymphohistiocytosis (HLH) was highly suspected based on criteria from the HLH-2004 trial [2]. According to HLH-94 protocol, intra-venous immunoglobin (IVIG, 1 g/kg per body weight, administered for 2

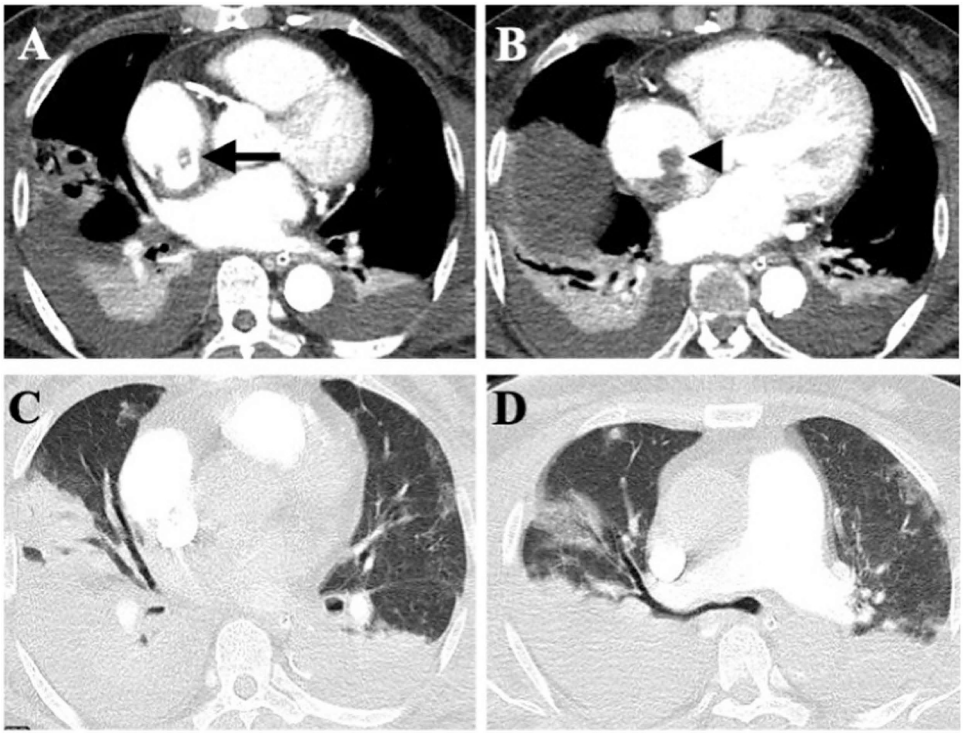

Fig. 1. A compilation of four computed tomography images done with dynamic injection of contrast medium of great vessel in chest. In both images a and b, thrombus in superior vena cava (arrow) and right atrium (arrowhead) were seen, respectively. In images c and d, acinar consolidation in right upper lobe, left upper lobe, and right middle lobe without presence of lung abscess.

Table 2
Laboratory values on admission and in ICU.

	On admission	In ICU	Normal range
Hemoglobin, (g/dL)	11.5	10.9	11 −16
Platelets, ($\times 10^9$/L)	115	43	140 −450
White blood cell, ($\times 10^9$/L)	30.3	0.7	4.0 −10.0
Aspartate Aminotransferase, (U/L)	33	174	15 −41
Alanine Aminotransferase, (U/L)		27	14 −40
Total Bilirubin, (mg/dL)		2.1	0.3 −1.2
Direct Bilirubin, (mg/dL)		1.5	0.1 −0.5
Prothrombin Time, (seconds)		10.4	9.7 −11.8
Activated Partial Thromboplastin Time, (seconds)		42.1	24.6 −31.2
Lactate Dehydrogenase, (U/L)		708	140 −271
Ferritin, (ng/mL)		1236.5	14 −165
D-dimer, (mg/L)	18.3	13.8	< 0.5
Fibrinogen, (g/L)		4.52	1.70 −4.20
Triglycerides, (mmol/L)		1.89	0.40 −1.69

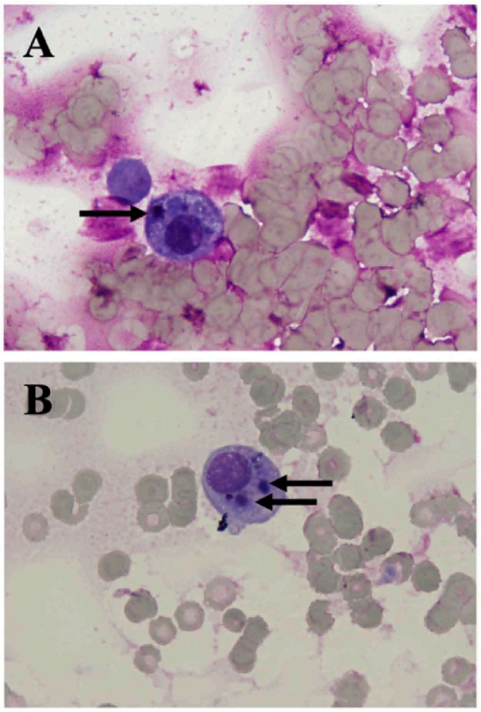

Fig. 2. A compilation of two photomicrographs from the bone marrow aspirate with a Liu's stain at 1000x magnification. In both images a and b, Erythrocytes that are phagocytosed by histiocytes are highlighted by the arrows.

days) and methylprednisolone 80 mg per day (near equivalent dose of dexamethasone 10 mg/m2/day in the initial 3 weeks) were administered since day 21 of admission. Etoposide was omitted due to severe infection. However, despite interventions above, she experienced progressed neutropenia and shock, requiring hemodynamic support with multiple vasopressors and inotropes, continued dependence on mechanical ventilator, and renal replacement therapy with Continuous Veno-Venous Hemodialysis (CVVH). Patient eventually expired on day 24 of admission. Final pathology of bone marrow showed severe hypocellular marrow for age (< 5 %) with depleted myeloid and erythroid lineage and hemophagocytosis (Fig. 3). Erythrophagocytosis was focally noted and consists of histiocytes that phagocytized extravasated, old, and/or damaged erythrocytes. EBER immunostain was negative, while no microorganism (in Periodic Acid-Schiff stain), blasts (in CD34 and CD117 stain), neoplasm or virus inclusion was found. Reticulin stain found no myelofibrosis. Although not fully

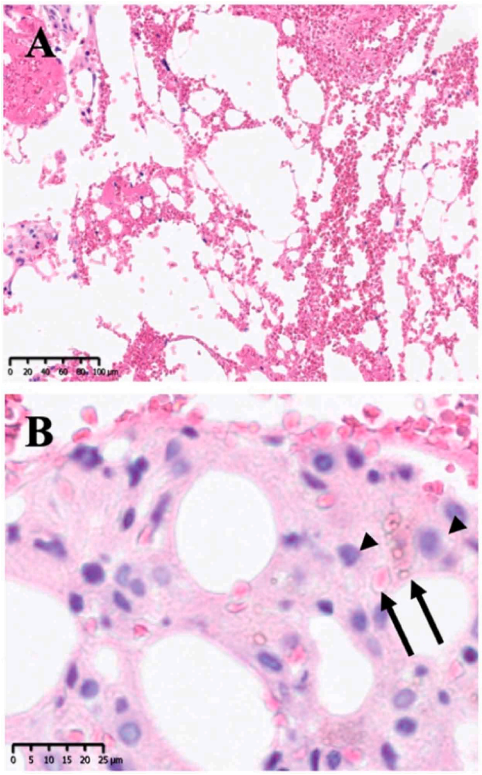

Fig. 3. A compilation of two photomicrographs from the bone marrow biopsy with a hematoxylin and eosin (H&E) stain. In image a, severe hypocellular marrow for age (< 5 %). In image, b, erythrophagocytosis is focally noted and consists of histiocytes (arrowheads) that phagocytize extravasated, old, damaged erythrocytes (arrows).

meeting the diagnostic criteria of HLH-2004, the HScore of this patient was 200, which indicated 88 % probability of HLH.

Systemic review

We systemically searched the PubMed database on cases of HLH associated with *Staphylococcus* infection. The following search terms were used: "hemophagocytic lymphohistiocytosis" OR "HLH" AND "*Staphylococcus aureus*". We searched the PubMed database on January 17, 2024. The search yielded 25 articles. Articles were included if they pertained to HLH and *Staphylococcus aureus*. We excluded articles in which the trigger factor of HLH were deemed to be unrelated to *Staphylococcus aureus*. Of the 25 articles, only seven case reports with nine patients were found relevant to our search (Table 3) [3–9]. The patients' ages ranged from 4 days to 59 years old and comprised of five males and four females. Both MSSA and MRSA infection was found. The most common preexisting disease was congenital heart disease in three patients. There was one patient with SLE and one patient with small cell lung cancer. The predominant primary infection was bacteremia in six cases. Patients also had pneumonia, urinary tract infection, and skin infection. *Staphylococcus aureus* were commonly found from blood cultures (8 patients). Two cases had *Staphylococcus aureus* isolated from bone marrow, one from cerebrospinal fluid, one from urine, one from sputum, and one from skin. Patients commonly received vancomycin, linezolid, and teicoplanin for treatment of MRSA, and cefazolin or amoxicillin-clavulanate for treatment of MSSA. The treatment for HLH included antibiotics and glucocorticoids for most patients, and included gamma globulin, hydroxychloroquine, anakinra, tocilizumab, and etoposide. Supportive transfusions were commonly given. Four patients died while five were cured. The results of the systemic review are delinated in Table 3.

Table 3
Systemic Review.

Author	DOI	Year	Case number	Age	Sex	Comorbidity	Primary infection
Ali	10.7759/cureus.49042	2023	1	7	F	Infective Endocarditis	Bloodstream infection
Li	10.1016/j.pedneo.2023.09.006	2023	3	1.3	M		Severe pneumonia
				1.6	F	Infective Endocarditis	Bloodstream infection
				12.9	M	Infective Endocarditis	Bloodstream infection
Hardage	10.12659/AJCR.934092	2021	1	43	M		bacteremia
Vedala	10.1177/2324709620974208	2020	1	67	M		bacteremia
Amisha	10.4103/jfmpc.jfmpc_190_19	2019	1	22	M		Urinary tract infection
Kaga	10.1620/tjem.240.167	2016	1	4 days	F		Skin
Hoshino	10.2169/internalmedicine.46.6378	2007	1	59	F		Pneumonia

Author	Preexisting disease	Staphylococcus aureus positive samples	Antibiotic used	Treatment	Outcome
Ali	Congenital heart disease	Blood culture	Vancomycin, meropenem	Transfusion	Expired
Li		Sputum and blood	Cefepime, Linezolid	Antibiotics + Glucocorticoids	Cured
	Congenital heart disease	Cerebrospinal fluid and blood	Cefotaxime, Meropenem, Ticoranine	Antibiotics + Glucocorticoids + Gamma globulin	Expired
	Congenital heart disease	Bone marrow and blood	Vancomycin, Meropenem, Linezolid, Rifampicin	Antibiotics + Glucocorticoids + Gamma globulin	Expired
Hardage	Systemic lupus erythematosus	Blood culture	Cefazolin	Corticosteroids, hydroxychloroquine, anakinra, tocilizumab, and low-dose etoposide as well as concomitant antibiotic therapy.	Cured
Vedala	Small cell lung cancer	Blood culture	Broad-spectrum antibiotics	Corticosteroids, antibiotics	Expired
Amisha	–	Urine, blood, bone marrow	Amoxicillin–clavulanate and gentamicin	Corticosteroids, antibiotic	Cured
Kaga	–	Skin	Vancomycin	Intravenous gamma globulin, platelet transfusion and vancomycin	Cured
Hoshino	–	Sputum and blood	Vancomycin, teicoplanin	Vancomycin, hemodialysis, short-term administration of corticosteroid	Cured

Diagnostic criteria (HS Score)

Author	Known underlying immunodeficiency	Peak temperature (°C)	Hepatomegaly	Splenomegaly	Low Hb level (g/dL)	Low leukocyte count (/mm3)	Low platelet count (/mm3)
Ali	–	unknown	–	+	+	–	+
Li	–	unknown	+	–	+	–	+
	–	unknown	+	–	+	–	+
	–	unknown	–	+	+	–	+
Hardage	+	unknown	+	+	+	+	+
Vedala	+	unknown	–	–	+	+	+
Amisha	–	unknown	+	+	+	+	+
Kaga	–	38.2 °C	–	–	–	–	+
Hoshino	–	39 °C	–	+	+	–	+

Author	High ferritin level (≥2000 ng/mL)	High triglyceride level (≥1.5 mmol/L)	Lower fibrinogen level (≤2.5 g/L)	High aspartate-aminotransferase level (≥30 IU/L)	Features of hemophagocytosis on a bone marrow aspirate	HS score (probability of HLH)
Ali	–	+	NA	–	NA	91
Li	+	–	+	NA	NA	112
	–	+	+	NA	NA	121
	–	+	–	NA	NA	121
Hardage	+	+	+	+	+	288
Vedala	+	+	NA	NA	NA	166
Amisha	+	+	NA	+	+	225
Kaga	–	NA	NA	–	NA	0
Hoshino	+	NA	NA	NA	+	150

NA: not applicable. + denotes presence of condition, - denotes absence of condition.

Diagnostic criteria (HLH−2004)

Author	Fever	Splenomegaly	Cytopenia	Fibrinogen (<1.5 g/L)	Hypertriglyceridemia (≥3.0 mmol/L)
Ali	+	+	+	NA	–
Li	+	–	+	+	–
	+	–	+	–	+
	+	+	+	–	+
Hardage	–	+	+	–	+
Vedala	+	–	+	NA	+
Amisha	+	+	+	NA	+
Kaga	+	–	(one cell line only)	NA	NA
Hoshino	+	+	+	NA	NA

Author	Hemophagocytosis on bone marrow aspirate	Low or absent natural killer activity	Ferritin (> 500 ng/mL)	Soluble CD25 (>2400 U/mL)
Ali	NA	NA	+	NA
Li	NA	+	+	NA
	NA	NA	+	NA
	NA	+	+	NA
Hardage	+	NA	+	NA

(*continued on next page*)

Table 3 (*continued*)

Vedala	NA	NA	+	NA
Amisha	+	NA	+	NA
Kaga	NA	NA	+	+
Hoshino	+	NA	+	NA

NA: not applicable. + denotes presence of condition, - denotes absence of condition.

Discussion

To the best of our knowledge, this is the first systemic review on the literature on HLH caused by Staphylococcus infection. We identified nine cases, ranging from infant to adults, in which three out of nine (33 %) had infective endocarditis. Mortality rate was 44 %, which was comparable to other causes of HLH.

Staphylococcus aureus is a rare cause of HLH. In a large national, retrospective cohort study performed in the US, HLH was most often associated with malignancy (30.7 %), followed by infections (24.3 %) [10]. Among 1108 cases of HLH caused by infections in a 2014 review, viruses account for 762 of the cases (68.8 %), while bacteria accounted for 206 (18.6 %), with *Staphylococcus* species accounting for only 15 out of the 1108 cases (1.4 %) [11].

HLH is difficult to diagnose, and especially hard in septic patients suffering from bacteremia. First, the sepsis condition itself may cause leukopenia, especially if complicated by disseminated intravascular coagulation (DIC). Additionally, many of the medications used to eliminate *Staphylococcus aureus* are associated with varying degrees of cytopenias. Vancomycin is associated with agranulocytosis, neutropenia, and pancytopenia [12–14]. Daptomycin may cause thrombocytopenia. Linezolid well known for association with myelosuppression which is dose and duration-dependent [15]. Thrombocytopenia post treatment with linezolid is especially common. Amoxicillin is associated with agranulocytosis, anemia, eosinophilia, immune thrombocytopenia, leukopenia, neutropenia [16], thrombocytopenia. In our patient, the diagnosis is further complicated by the fact that anemia, thrombocytopenia, and leukopenia had different time of onset and course of progression. In a postmortem clinicopathologic analysis conducted by Strauss et al., it was found that routine peripheral blood cell counts could not reliably predict if patients may have HLH [17]. However, La Rosée P et al. have strong consensus that in critically ill patients with persistent fever, cytopenias, and organomegaly, particularly in confirmed or presumed cases of sepsis, sepsis-like syndromes, and/or evolving multiorgan failure, suspicion for HLH should be raised and further HLH testing should be initiated [18].

It's worth noting that in our patient, cytopenias emerged subsequent to the clearance of MRSA from blood cultures. This occurrence is likely linked to the pathophysiology of HLH. Given that HLH is an immune-mediated disorder, the inflammatory cascade seems to endure even after the elimination of the primary inciting factor. This persistent inflammatory response can catch clinicians off guard; just when they may feel reassured by the apparent improvement in the patient's condition, there's a sudden downturn, and in fact in our patient it was HLH, rather than the initial infection, that caused her ultimate demise. In our case, the bacteremia had initially been hard to eradicate; this is mirrored in the cases found in our review, in which 3 out of 9 had infective endocarditis, which is also characterized by having a foci of infection which is hard to eliminate. Prolonged, stubborn infections appear to trigger inflammation and immune activation, leading to HLH, a response that persists even after the removal of the initial trigger.

In managing HLH, a triple simultaneous approach is crucial, encompassing supportive care for its often life-threatening manifestations, identification and removal of trigger factors, and suppression of the inflammatory response and cell proliferation through the use of immunosuppressive and cytotoxic drugs. If the trigger factor is infection-related and not attributed to a virus or Leishmaniasis, corticosteroids, with or without intravenous immunoglobulin, are typically recommended. However, due to the patient's advanced renal failure and critical illness, chemotherapy such as etoposide was not administered, as it could potentially exacerbate end organ damage caused by the cytokine storm in HLH and its chemotherapy. Regarding mortality rates associated with different etiologies, patients with sepsis and ICU admission may face a mortality rate ranging from 51 to 67 %. Despite aggressive intervention and successful eradication of MRSA bacteremia, the development of HLH ultimately led to the patient's death [19].

Conclusion

HLH triggered by Staphylococcus infection is rare but life-threatening, demanding a high level of clinical suspicion. Effective management typically entails a combination of immunosuppressive, biological, and supportive treatments, and in some cases, even hematopoietic stem cell transplantation. Our case underscores the importance of maintaining heightened vigilance when treating prolonged MRSA infections and recognizing the potential for HLH, even after the bloodstream has been cleared of bacteria.

CRediT authorship contribution statement

Shih-Hao Chung: Writing – original draft. **Yen-Yu Liu:** Writing – review & editing, Conceptualization. **Shih-Ya Huang:** Writing – review & editing. **Meng-Ta Sung:** Writing – review & editing, Conceptualization. **Alice Ying-Jung Wu:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Conflict of interest statement

fThe authors declare no conflict of interest. This study was reviewed by the Institutional Review Board of MacKay Memorial Hospital with IRB approval number 24MMHIS068e.

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