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ID TEACHING CASES

A Case of Hemophagocytic Lymphohistiocytosis Associated With Mediterranean Spotted Fever in a Healthy 29-Year-Old Female

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A 29-year-old female presented with fever, headache, and epigastric pain. Though her initial presentation was benign and nonspecific, she soon developed a full-blown cytokine storm with disseminated intravascular coagulation. She was diagnosed with hemophagocytosis secondary to *Rickettsia conorii* infection. A good outcome was achieved thanks to prompt diagnosis and proper treatment.

Keywords. hemophagocytosis; Mediterranean spotted fever; *Rickettsia*.

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening syndrome caused by excessive immune activation and cytokine storm [1, 2]. Cardinal features include fever, hepatosplenomegaly, cytopenias, and histological hemophagocytosis [1, 3].

Primary genetic HLH is caused by a mutation in a component of the perforin-mediated cytotoxicity pathway and may be either familial or associated with genetic immunodeficiency syndromes (Chediak-Higashi, Griscelli type-2, and X-linked lymphoproliferative disorder) [4]. Most commonly it affects infants, and it may also be triggered by a viral infection, particularly Epstein Barr virus (EBV) [4]. Secondary or acquired HLH may occur in adults sporadically, in association with many triggers, namely infectious, autoimmune, and malignant diseases [3]. It is believed that the incidence of secondary HLH has been rising in recent years, perhaps due to increased awareness.

In the absence of a proven relevant mutation, the Henter 2004 criteria have been proposed and are commonly applied to diagnose HLH [3, 5, 6].

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We describe a case of acquired HLH secondary to Mediterranean spotted fever (MSF) caused by *Rickettsia conorii* in a 29-year-old healthy female in the North of Israel. The clinical manifestations, workup, differential diagnosis (DD), and outcome in this patient are described and discussed.

CASE REPORT

A 29-year-old Jewish female presented to the emergency room at the Galilee Medical Center Nahariya in Northern Israel with a 1-week history of headache and 3 days of fever (>38.5°C). She had also complained of diarrhea lasting 2 days at a prior presentation that had resolved spontaneously. She had been previously healthy with an uneventful medical history. At presentation, she was tachycardic (122 bpm) with fever (38.7°C). Otherwise she was in a good clinical shape, with no alarming signs. Her laboratory results were unremarkable (Table 1). Her beta HCG was negative. She was symptomatically treated with clinical improvement and subsequently discharged with a presumed diagnosis of a mild viral illness.

Two days later, she returned with persisting complaints of headache, fever, and chills. In addition, she mentioned epigastric pain, nausea, and vomiting. She had been self-medicating with ibuprofen for 3 days. Except for tachycardia (140 bpm), her vital signs were normal. Blood tests revealed a normal white blood cell count and hemoglobin (Hb), but she now had thrombocytopenia (Platelets [PLT] 126 $\times 10^3$/uL), mild hyponatremia (132 mmol/L), and hypokalemia (2.98 mmol/L) with a C-reactive protein of 270 mg/L (Table 1). Chest and abdominal x-rays were unrevealing. Due to persisting symptoms and abnormal labs, she was admitted for further evaluation.

Upon admission, she was tachycardic (146 bpm) with a fever of 38°C. In repeated anamnesis, she denied any travels, exposure to unhealthy individuals, or contact with animals. On physical examination, there was only mild epigastric tenderness without rebound. Blood cultures and viral serologies were drawn. Due to increased hepatocellular enzymes and slightly increased bilirubin (Table 1), the DD included viral hepatitis, acute cholecystitis/cholangitis, or a liver injury secondary to nonsteroidal anti-inflammatory drugs. An abdominal ultrasound showed only a normal size gallbladder with thickened walls (1 cm). Acute cholecystitis was the most likely diagnosis. Ceftriaxone and metronidazole were initiated. Twelve hours later, she began deteriorating: Her blood pressure dropped, and lab tests showed metabolic acidosis, acute kidney injury, hepatocellular and cholestatic injury with rising bilirubin, prolonged PT, and low fibrinogen (169 mg/dL). She had anemia (Hb 9.7 g/dL), deteriorating thrombocytopenia (52 $\times$ 10^3/µL), and leukocytosis with a left shift (Figure 1). Schistiyocytes were

Table 1. Laboratory Findings at First Emergency Room Presentation (Day 0), at Second ER Presentation, During Admission, and After Recovery (Day 14)

		At First ER Presentation	At Second Presentation to the ER and During Admission				Recovery
	Normal Range	Feb 28 (Day 0)	March 2 (06:21)	March 2 (20:02)	March 3 (03:45)	March 3 (15:34)	April 14
Hb, g/dL	12–16	12.4	12.9	11.7	9.7	11	10.8
PLT, $\times 10^3$/μL	130–400	268	126	52	39	42	280
WBC, $\times 10^3$/μL	4–10	7.73	9.14	12.26	12.74	17.75	8.39
BUN, mg/dL	7–19	5.6	6.10	18.5	24.4	31.6	16.2
Cr, mg/dL	0.57–1.11	0.7	0.68	2.33	2.7	3.04	0.62
Na+, mmol/L	136–145	137	132	136	136	137	NA
K+, mmol/L	3.5–5.1	3.26	2.98	3.62	3.72	3.32	NA
CRP, mg/L	0.2–5	108	273	NA	254	316	6.8
Bil. total, mg/dL	0.2–1.2	0.41	2.14	3.01	3.55	4.09	0.56
Bil. direct, mg/dL	0.1–0.5	NA	1.7	2.51	2.89	3.47	NA
LDH, U/L	125–243	NA	475	707	657	942	237
AST, U/L	5–34	73	173	224	178	251	26.5
ALT, U/L	0–55	NA	150	143	111	136	62.1
ALP, U/L	40–150	NA	119	91	85	95	60
GGT, U/L	9–36	NA	NA	109	86	NA	79.4
Albumin, g/dL	3.5–5	NA	2.99	2.66	2.95	2.74	3.76
PT, sec	9–14	NA	NA	23.6	20.2	19.5	NA
INR	0.8–1.2	NA	NA	2.1	1.8	1.7	NA
D-dimers, ng/mL	0–500	NA	NA	64 579	NA	71 395	NA
Ferritin, ng/mL	15–150	NA	NA	NA	NA	10 908[a] 12 478[b]	351
Fibrinogen, mg/dL	200–430	NA	NA	169	NA	142	NA
TG, mg/dL	–150	NA	198.7	NA	472	523.2	424

During admission, anemia, thrombocytopenia, coagulopathy, liver and kidney injury, hypoalbuminemia, and hyperferritinemia are evident. The following rheumatologic and infectious serologies were all negative: ANA, antismith Ab, anti-RO, anti-LA, anti-RNP70, anti-RNP, anti-Jo1, anti-Scl70, anticentromer, anti-CCP, RF, complement, C-ANCA, P-ANCA, ASLO, parvovirus B19, HCV, HBV, HIV, *Brucella*, Q fever, syphilis, leptospirosis (serologies and PCR), *Rickettsia typhi* murine typhus (IgM and IgG), and *Rickettsia conorii* spotted fever (IgM and IgG). EBV and CMV serologies were compatible with a past infection (EBV VCA IgM negative, EBNA Epstein-Barr nuclear antigen IgG positive, CMV IgG positive, CMV IgM negative).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; anti-RNP, anti-ribonucleoprotein; anti-RNP70, anti-ribonucleoprotein70; ANA, Anti Nuclear Antibody; ASLO, antistreptolysin O; AST, Aspartate transaminase; BUN, Blood urea nitrogen; C-ANCA, Cytoplasmic Anti neutrophil cytoplasmic antibodies; CCP, Anti-cyclic citrullinated peptide; Cr, Creatinine; CRP, C-reactive protein; CMV, cytomegalovirus; EBNA, Epstein-Barr nuclear antigen; EBV, Epstein Barr virus; ER, Emergency room; GGT, Gamma-glutamyl transferase; Hb, hemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; IgG, immunoglobulin G; IgM, immunoglobulin M; INR, international normalised ratio; P-ANCA, perinuclear-anti neutrophil cytoplasmic antibodies; PCR, polymerase chain reaction; PLT, platelets; PT, prothrombin time; RF, rheumatoid factor; TG, Triglycerides; VCA, viral capsid antigen; WBC, white blood cell count.

[a]First measurement.

[b]Second measurement.

observed on a blood smear. A diagnosis of disseminated intravascular coagulation (DIC) was made, and she was treated with fresh frozen plasma and cryoprecipitate. Following blood product transfusion, the patient stabilized. She later developed skin necrosis on the dorsal side of her feet and was treated with intravenous heparin.

An urgent computed tomography scan excluded emphysematous cholecystitis or visceral perforation as a cause of DIC. Significantly thickened gallbladder and periportal edema were demonstrated. Re-evaluating the DD, a wide battery of serological tests was taken (Table 1). Sepsis was the most likely diagnosis. Due to thrombocytopenia, hyponatremia, and headache, an atypical infection such as rickettsiosis was considered, and doxycycline treatment was empirically initiated. Interestingly, ferritin levels were dramatically elevated (12 478 ng/mL), and fibrinogen levels were still particularly low (142 mg/dL). A bone marrow biopsy performed on day 4 of admission exhibited evident hemophagocytosis (Figure 2). Natural killer (NK) cell activity was preserved (71%), but soluble IL-2 receptor (sIL-2R) levels were elevated (11 978 U/mL; normal: 300–2000 U/mL). A diagnosis of HLH was established.

As there was no family history of primary HLH, immune deficiencies, or perforin pathway mutations, a plethora of possible triggers was evaluated. Rheumatologic and infectious serologies were all negative (Table 1). ADAMTS-13 antibodies and activity were within the normal range. Blood, urine, and stool cultures were also negative. Blood polymerase chain reaction (PCR) was positive for *Rickettsia conorii*.

The HLH-94 treatment protocol (dexamethasone and etoposide) was immediately initiated, in addition to doxycycline. Subsequently, the patient gradually improved during the next few weeks, and her labs normalized (Figure 1).

DISCUSSION

An increasing number of acquired HLH cases have been reported in recent years [3]. However, it has been suggested that HLH may go undiagnosed due to a varying clinical

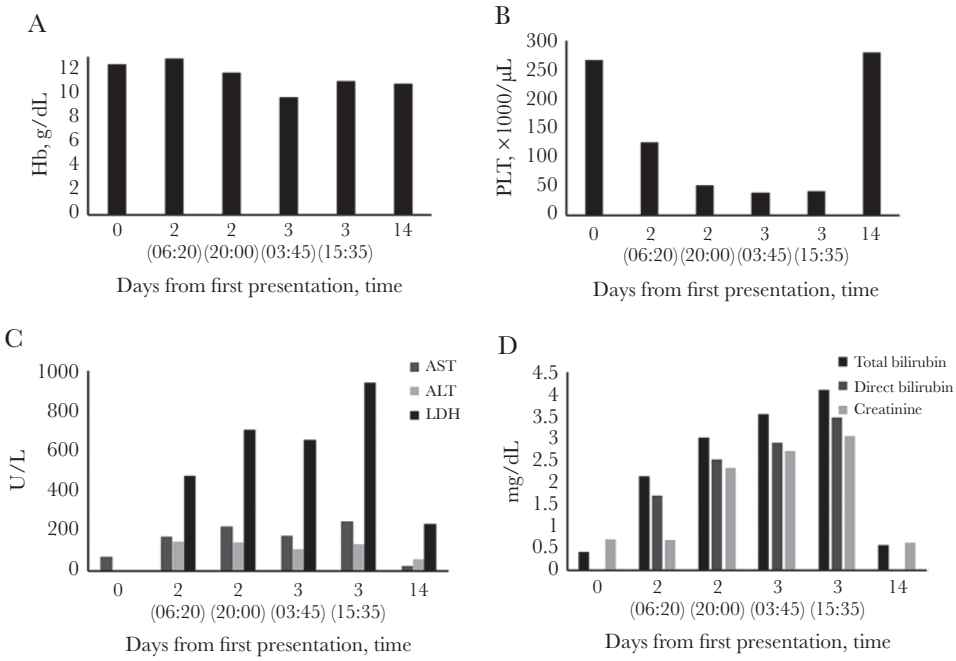

Figure 1. A graphic summary of the most prominent laboratory results in time from the first presentation to the emergency room (day 0) until recovery (day 14). A, Hb levels. B, Platelets. C, Hepatocellular liver enzymes and lactate dehydrogenase. D, Bilirubin (total and direct) and creatinine levels. The graphs demonstrate anemia, thrombocytopenia, acute liver injury, and acute kidney injury. Values practically returned to baseline following treatment, on day 14. Abbrevations: ALT, Alanine transaminase; AST, Aspartate transaminase; LDH, Lactate dehydrogenase.

presentation, poor reproducibility of the Henter criteria, and insufficient awareness in medical caregivers of this syndrome [7]. Indeed, several challenges might hinder diagnosis [8]: First, the HLH-2004 diagnostic criteria were initially developed based on pediatric familial cases, and even though widely applied, they have not been validated in adults or in secondary HLH. Second, many diagnostic criteria are nonspecific (fever, cytopenias, hypofibrinogenemia) and may be encountered

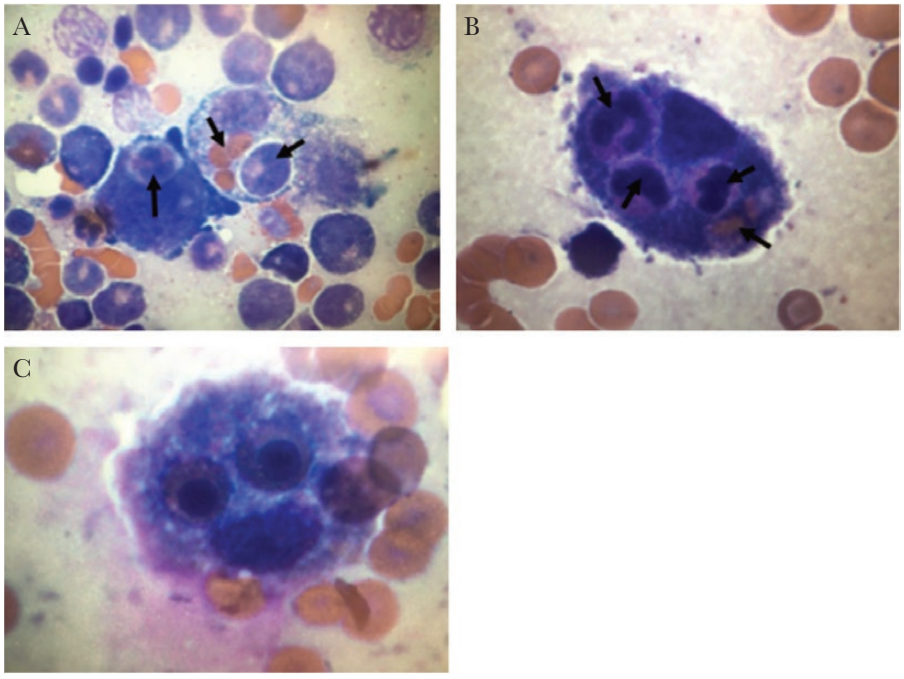

Figure 2. Bone marrow biopsy showing phagocytosis of red blood cells and polymorphonuclear cells, as indicated by the arrows.

in infections and hematologic malignancies without HLH. Contrarily, HLH patients frequently exhibit findings other than those included in the diagnostic criteria (hypoalbuminemia, elevated liver enzymes, coagulopathy). The clinical overlap between HLH, sepsis, and multi-organ dysfunction syndrome may lead to HLH misdiagnosis, particularly in an intensive care unit setting. Finally, without specific markers such as sIL-2R levels, NK cell activity, or histological hemophagocytosis, these syndromes could be clinically indistinguishable. Needless to say, these markers are neither tested routinely nor readily available at medical centers [8, 9].

In the present case, the clinical presentation was indeed nonspecific and dynamic. Through the course of illness, the patient developed clinical and radiologic findings suggestive of acute acalculus cholecystitis. Retrospectively, these findings could be explained by periportal and hepatic infiltration of macrophages and lymphocytes [10].

Upon deterioration, she was re-evaluated, and a comprehensive DD was considered. Fever and multi-organ failure in a previously healthy individual are attributed with a high probability to sepsis. As already mentioned, sepsis is a great mimicker of HLH. Padhi et al. previously reported that in 4 out of 7 reviewed cases of secondary HLH, a diagnosis of sepsis was initially presumed [7]. In the present case, the dramatic rise in ferritin beyond 10 000 ng/mL ("sky high" hyperferritinemia) was suggestive of HLH [11].

Microangiopathic hemolytic anemia and thrombocytopenia could also be attributed to hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). However, the multi-organ failure combined with coagulopathy could not be well explained by HUS or TTP. Nevertheless, a normal ADMATS13 activity ruled out TTP.

Although diagnosis of HLH is quite challenging, our patient eventually fulfilled 6 of the 8 Henter criteria: fever, bicytopenia, hyperferritinemia, hypertriglyceridemia with hypofibrinogenemia, histologic hemophagocytosis, and elevated sIL-2R levels.

When HLH diagnosis was established, a trigger was sought. PCR was positive for *Rickettsia conorii,* although serologies were negative. This was attributed to the fact that serologies were examined early during the disease course (day 9/10 since initial symptom onset).

Early manifestations of MSF commonly include fever, headaches, myalgias, and sometimes nausea and vomiting. A maculopapular rash usually follows, predominantly on the palms and soles, with *Rickettsia conorii*. Occasionally an inoculation eschar may be found [12]. Thrombocytopenia, leukopenia, hyponatremia, and increased hepatocellular enzymes are common findings [13–16]. Indeed, our patient presented with many of these symptoms. However, rash and eschar were not found. In a study by Lecronier et al., in only 1 out of 9 MSF cases was a rash not present [17, 18]. In Israel, the common variant is Israeli spotted fever (ISF) caused by *Rickettsia conorii* subsp. *israelensis*. The clinical manifestations are similar to MSF; however, tick exposure is reported in 32%, and an eschar is rarely observed (38%) [12]. Unfortunately, sequencing for the specific subspecies of *Rickettsia conorii* was not performed in the present case.

Ramos-Casals reported a total of 2197 identified cases of adult HLH in the literature, half of which were triggered by infections [3]. Most cases of bacteria-associated HLH were due to intracellular organisms, primarily Tb. Notably, <20 cases of HLH secondary to MSF have been reported [17–23] (Table 2). Most cases were reported in France [17, 19, 20], with others in Spain [21], Italy [22], and Sri Lanka (Table 2) [18]. In nearly all cases, patients presented with fever and a maculopapular rash. Headache, nausea, vomiting, and myalgia were also prevalent. Interestingly, 1 of the earliest HLH cases caused by *Rickettsia conorii* was reported in Israel in 1989 [23]. Israel is an endemic country of *Rickettsia conorii* [24]. Thus, in the present case doxycycline was initiated early and based on clinical suspicion only, even though the classical rash and exposure were absent. This clinical approach turned out to be life-saving.

Other pathogens from the *Rickettsia* family have also been associated with HLH (Table 2) [25]. In fact, HLH has been primarily reported with scrub typhus and ehrlichiosis and to a lesser extent with *Rickettsia conorii* and *Rickettsia Japonica* (Table 2) [26, 27]. A recent comprehensive review on scrub typhus–associated HLH identified 30 cases, all in the Far East [28]. In adults, treatment mostly relied on *Rickettsia*-specific antibiotics, while only in 25% were other treatments added (Table 2). As for ehrlichiosis-induced HLH, there are substantial reports [29–41], mostly in the United States. Ten cases in immunocompetent adults have been reported with a good outcome upon doxycycline treatment (Table 2) [32].

The pathogenesis of *Rickettsia*-induced HLH is not completely elucidated. The underlying common mechanism in both genetic and reactive HLH is a defective granule-mediated cytotoxicity. Uncontrolled activation of T cells and antigen-presenting cells (macrophages and histyocytes) is thought to be caused by enhanced antigen presentation and continuous stimulation of toll like receptors by interferon-γ [2, 3]. *Rickettsia* is an intracellular pathogen. As such, following phagocytosis, it may trigger an inappropriate Th-1 response, activating macrophages and significant cytokine release. Concurrent deficient cytotoxicity of NK and CD8 cells may result in persistent lymphocyte and histyocyte activation and excessive levels of tumor necrosis factor–α, interferon-γ, macrophage colony-stimulating factor, interleukin (IL)-1, IL-4, IL-6, IL-10, and IL-18, all important markers of the cytokine storm seen in HLH [3].

Treatment of HLH is generally based on support measures, trigger elimination, and immunosuppressive therapy. However, currently, there are no randomized controlled

Table 2. A Summary of All Published Cases of *Rickettsia*-Associated HLH

Reference	Species	Numbers, Age	Geography	Clinical and Laboratory Presentation	Treatment	Outcomes
Present case	MSF	1 case 29 y	Israel	Fever, headache, diarrhea, epigastric pain, nausea, vomiting, anemia, thrombocytopenia, AKI, ALI, DIC	Doxycycline HLH-94 protocol	Recovery
Berner [23]	MSF	1 case 30 y	Israel	Fever, myalgia and arthralgia, nausea, vomiting, maculopapular rash (palms and soles), anemia, thrombocytopenia	Tetracycline	Recovery
Lecronier [17]	MSF QF	9 cases 8 adults 1 pediatric 8 cases	France	Fever, maculopapular rash or purpura, anemia and thrombocytopenia in most cases	Doxycycline in all Additional Rx: ceftriaxone (13%), levofloxacin (13%), hydroxychloroquine (6%), IVIG (13%), CCS (6%)	Recovery
Premaratna [18]	MSF	1 case 37 y	Sri Lanka	Fever, pallor, lymphadenopathy, splenomegaly, anemia	Doxycycline	Recovery
Sotto [19]	MSF	1 case 42 y	France	Fever, headache, myalgia and arthralgia, maculopapular pruritic rash, thrombocytopenia	Doxycycline	Recovery
Bertrand [20]	MSF	2 cases 77 y, 63 y	France	Fever, macculo-purpuric rash, inoculation ulcer	NA (article in French)	NA
Perez-de Pedro [21]	MSF	1 case 38 y	Spain	Fever, headache, myalgia, nausea, vomiting, maculopapular rash (palms and soles), splenomegaly, anemia, thrombocytopenia	Doxycycline, levofloxacin, cyclosporin, dexamethasone	Recovery
Cascio [22]	MSF	1 case 5 y	Italy	Fever, maculopapular rash on palms and soles, splenomegaly, anemia, thrombocytopenia	Chloramphenicol and clarithromycin	Recovery
Kaneko [26]	JSF	1 case 71 y	Japan	Fever, rash, vomiting, thrombocytopenia, petechiae, AKI, hyperbilirubinemia, DIC	Minocycline and levofloxacin Intubation, vasopressors, steroids, hemodiafiltration, blood products	DIC and death
Otsuki [27]	JSF	1 case 3 mo infant	Japan	Fever, loss of appetite, macular rash, hepatosplenomegaly, thrombocytopenia, anemia	Minocycline, IVIG	Recovery
Naoi [28]	Scrub typhus	30 cases 17 adults 13 pediatric	India (33%) China (30%) Japan (20%) South Korea (6.7%) Taiwan (6.7%) Sri Lanka (1%)	Fever, rash/eschar, hepatosplenomegaly, liver dysfunction, anemia, thrombocytopenia, hyperferritinemia	In all 30 cases: doxycycline/azithromycin/ clarithromycin/ chloramphenicol 25% of adults and 69% of pediatrics: + IVIG/steroids In only 3 cases: + chemotherapy	Recovery 93% (1 case with sequelae) with single antibiotic: nearly 50% cure 6.7% mortality
Patel [32]	HME	1 case 65 y	USA (Missouri)	Fever, headache, splenomegaly, leukopenia, anemia, thrombocyto-penia, hyperferritinemia, AKI, respira-tory failure	Doxycycline	Recovery
Otrock [33]	HME	5 cases (adults)	USA	Fever, cytopenias, hypertriglyceridemia, and high ferritin	Doxycycline	Recovery
Kaplan [34]	HME	1 case 41 y	USA (Northern Illinois)	Fever, malaise, encephalitis, anemia, thrombocytopenia, hyperferritinemia, AKI	Doxycycline Prednisone IVIG	Recovery

Table 2. Continued

Reference	Species	Numbers, Age	Geography	Clinical and Laboratory Presentation	Treatment	Outcomes
Kumar [35]	HME	1 case 63 y Immunosuppressed (renal transplant)	USA (Alabama)	Fever, altered mental status, hepatosplenomegaly, anemia, thrombocytopenia, hyperferritinemia, AKI, hepatocellular injury	Doxycycline Anakinra High-dose corticosteroids	Recovery
Pandey [36]	HME	1 case 74 y (RA on DMARDs)	USA	Fever, thrombocytopenia, hyperferritinemia, toxic shock–like syndrome, oliguric renal failure	Doxycycline	Recovery
Badireddi [37]	HME	1 case 74 y	USA	Fever, dyspnea, nausea, lethargy, AKI, liver injury, coagulopathy, anemia, thrombocytopenia, hyperferritinemia	Doxycycline	Recovery
Provenzano [38]	HME	1 case 47 y	USA	Fever, thrombocytopenia, hyperferritinemia	Doxycycline HLH-directed therapy	Recovery
Naqash [39]	HME	1 case 66 y Immune-compromised (HIV)	USA	Fever, lethargy, abdominal pain, pancytopenia, AKI, hepatocellular injury, hyperferritinemia	Antibiotics + amphotericin B Etoposide and dexamethasone (doxycycline withheld due to past severe angioedema-like reaction)	Death

Abbreviations: AKI, acute kidney injury; ALI, acute liver injury; CCS, Corticosteroids; DIC, disseminated intravascular coagulation; DMARDs, Disease modifying anti-rheumatic drugs; HLH, hemophagocytic lymphohistiocytosis; HME, human monocytic ehrlichiosis (*Ehrlichia chaffeensis*); JSF, Japanese spotted fever (*Rickettsia japonica*); IVIG, intravenous immunoglobulin; MSF, Mediterranean spotted fever (*Rickettsia conorii*); NA, not available; QF, Q fever (*Coxiella burnetii*); RA, Rheumatoid arthritis; scrub typhus (*Orientia tsutsugamushi*).

trial–based guidelines regarding the ultimate treatment protocol in adults. Therapeutic decisions are practically based on clinical experience, expert opinion, and on a case-by-case approach [3]. The HLH-94 protocol has been mainly established as a consensus for primary genetic HLH [42]. In adults, treatment of secondary HLH should be tailored according to the underlying trigger. A treatment algorithm has been recently suggested by La Rosée et al. [42]: In clinically stable patients, it is acceptable to specifically target treatment to the underlying condition. However, in deteriorating patients, corticosteroids may be initiated with the possible addition of intravenous immunoglobulin (IVIG). A clear indication for immediate etoposide administration is severe HLH presenting with imminent organ failure [42]. Upon trigger identification, several additional treatments are possible: in EBV-associated HLH, virostatics and rituximab may be added. In leishmaniasis-associated HLH, liposomal amphotericin B is suggested. Cytokine-directed agents (anti-IL1, anti-IL6) have emerged in recent years as add-on treatments in macrophage-activating syndrome (MAS; ie, HLH secondary to rheumatologic conditions). Conventionally, MAS is treated with pulse steroids, with the possible addition of cyclosporin A and anakinra (anti-IL1) [42]. Etoposide may be added in nonresponsive cases. Tocilizumab (anti-IL6) may be used in MAS and drug-induced HLH [42]. Tocilizumab has also been reported as an adjuvant therapy for HLH associated with visceral leishmaniasis [43] and has been recently employed to treat the HLH-resembling hyperinflammation associated with sepsis and COVID-19 [44–46].

There is a strong consensus that HLH induced by intracellular infections (tuberculosis, leishmaniasis, rickettsiosis) usually does not need HLH-94 treatment [42]. Notably, most reported cases of rickettsiosis-associated HLH have been successfully treated with only specific antibiotics (mostly doxycycline). However, in acutely ill deteriorating patients, treating the underlying infection may not always be sufficient. In a few reported cases, corticosteroids, IVIG, and occasionally anakinra were added (Table 2).

Although prognosis varies between studies, if left untreated, HLH is invariably fatal. In adults, prognosis is worse in those with an underlying malignancy (particularly lymphoma), alcoholism, G6PD deficiency, age >50 years, neurologic involvement, and high ferritin with a slow decline [22, 47–49]. Specifically, the prognosis of MSF-associated HLH may depend on the specific *Rickettsia* subspecies, the delay in antibiotic treatment, and the use of immunosuppressive drugs [22]. An excellent outcome has been reported in MSF-associated HLH, in most cases without additional treatment other than antibiotics [17–23]. Nevertheless, as our patient presented with rapidly deteriorating multi-organ failure and DIC, an aggressive treatment approach was opted for.

DIC is considered a severe complication and has been previously reported as an independent predictor of high mortality in HLH [7]. Here, DIC was diagnosed early. Skin gangrene in the lower extremities also indicated the severity of our patient's disease. Cohen et al. reported a case of ISF complicated by DIC and purpura fulminans where the patient eventually died [16]. Similarly, a case of JSF complicated by HLH and DIC was fatal despite maximal treatment [26]. In contrast, a good outcome was achieved here. This may be attributed to the patient's young age, baseline well-being, early recognition and treatment of DIC, and most importantly prompt initiation of doxycycline and the HLH-94 protocol.

CONCLUSIONS

HLH is an elusive clinical syndrome. This case underscores the importance of having a high index of suspicion both for HLH and for MSF as a triggering infection in endemic areas, even when the classical rash and exposure details are lacking.

Acknowledgments

Potential conflicts of interest. There are no conflicts of interest to declare. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Patient consent. The patient's consent was obtained.

Ethical approval. A local ethical committee approval does not apply in this case.

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