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SEVERE SECONDARY HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SYNDROME DUE TO CRIMEAN-CONGO HAEMORRHAGIC FEVER VIRUS: THINKING OUT OF THE BOX

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ABSTRACT

Introduction: Crimean-Congo haemorrhagic fever is an acute, often severe haemorrhagic disease caused by the homonymous virus. On the other hand, severe life-threatening secondary haemophagocytic lymphohistiocytosis is a rare entity usually associated with underlying haematological malignancies, infectious or autoimmune diseases. Herein, we report a fatal case of severe secondary haemophagocytic lymphohistiocytosis due to the abovementioned virus but also a second case of Crimean-Congo haemorrhagic fever with virus-induced threatening haemophagocytic lymphohistiocytosis in an internist who was responsible for the patient's management.

Case description: A 72-year-old stockbreeder progressed to fatal secondary haemophagocytic lymphohistiocytosis due to Crimean-Congo haemorrhagic fever virus (fever, hepatosplenomegaly, severe cytopenias, low fibrinogen, hypertriglyceridemia and extremely high ferritin levels), despite aggressive supportive measures and specific treatment with corticosteroids and intravenous γ-immunoglobulin. The second case was a 54-year-old internist who acquired the Crimean-Congo haemorrhagic fever virus through mucocutaneous exposure to the patient's blood, recovering fully with prompt double treatment against active viral replication and early stage haemophagocytic lymphohistiocytosis.

Discussion: Crimean-Congo haemorrhagic fever virus is a rare cause of secondary haemophagocytic lymphohistiocytosis with an unfavourable outcome if the patient has a rapidly progressing course as in our first case. Clinicians should maintain a high level of clinical suspicion in the appropriate clinical setting since prompt initiation of treatment for secondary haemophagocytic lymphohistiocytosis as in the second case, can be lifesaving.

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Conclusion: These cases emphasize that Crimean-Congo haemorrhagic fever virus can be a cause of severe life-threatening haemophagocytic lymphohistiocytosis even in non-endemic areas, while stringent infection control to prevent secondary healthcare-associated transmission is of the utmost importance.

KEYWORDS

Crimean-Congo haemorrhagic fever virus, haemophagocytic lymphohistiocytosis, haemophagocytic-ferritinemia

LEARNING POINTS

- Crimean-Congo haemorrhagic fever virus can be a rare cause of severe life-threatening haemophagocytic lymphohistiocytosis syndrome even in non-endemic areas
- Clinical suspicion for haemophagocytic lymphohistiocytosis due to Crimean-Congo haemorrhagic fever virus should be high in the appropriate clinical setting as prompt initiation of therapy can be lifesaving
- It is important to apply secondary prevention of healthcare-associated transmission of Crimean-Congo haemorrhagic fever.

INTRODUCTION

Crimean-Congo haemorrhagic fever (CCHF) virus, a member of the Orthonairovirus family is the causative agent of an acute, mostly severe disease, namely CCHF, characterized by high mortality rate (40-50%)[1]. CCHF has a wide geographical distribution: It is endemic throughout Africa, the Middle East, Southeast Asia, and parts of Europe, especially in the Balkans[1]. Clinical manifestations include fever, myalgias, headache, haemorrhagic features and multi-organ failure. In 2008, the first autochthonous CCHF case with a fatal outcome was reported in the northeastern part of Greece[2].

Secondary or acquired haemophagocytic lymphohistiocytosis is a rare, under-recognized, and potentially life-threatening hyperinflammatory syndrome characterized by fever, markers of systemic inflammation including a sharp increase of ferritin, low blood cell counts, central nervous system inflammation, disseminated intravascular coagulopathy, hepatitis, and high risk for progression to multiple-organ dysfunction, shock and often death because of uncontrolled massive proliferation of macrophages and T cells[3]. This syndrome can occur in any age group and is usually associated with underlying malignant, infectious or autoimmune rheumatic diseases, even though no underlying disease or any triggering factor is identified in some cases (idiopathic haemophagocytic lymphohistiocytosis)[3-5].

Herein, we report a fatal case of severe haemophagocytic lymphohistiocytosis due to CCHF virus, and also a second case of CCHF with virus-induced early stage haemophagocytic lymphohistiocytosis in an internist who was responsible for the patient's management.

CASE DESCRIPTION

On June 2025, a 72-year-old male stockbreeder with a history of bladder carcinoma treated by cystectomy and neobladder formation with bilateral nephrostomy tube placement two years ago, was admitted to our Department because of a 2-day history of high fever (>39.5°C), rigors and persistent frontal headache. The patient had no recent travel history and had already received antibiotic treatment (amoxicillin/clavulanate) from his primary care physician without improvement. On initial evaluation he was lethargic with high fever, tachycardia (110 bpm) and macroscopic haematuria. Laboratory tests revealed anaemia, significant thrombocytopenia, prolonged prothrombin and partial thromboplastin times, low fibrinogen, abnormal liver enzymes, very high ferritin and acute kidney injury *(Table 1)*. Computed tomography scan of the abdomen showed hepatosplenomegaly, and mild bilateral pelvicalyceal dilatation. Broad spectrum antibiotic treatment with piperacillin-tazobactam and teicoplanin was started after multiple sets of blood and urine cultures, for probable severe urinary tract infection. Gradually, the patient developed severe thrombocytopenia (platelets 6,000/µl) with progressively higher levels of lactate dehydrogenase (3,951 U/l), extremely high ferritin (105,707 ng/ml), and deteriorating renal and liver function *(Table 1)*. Empiric antibiotic treatment was escalated to meropenem, teicoplanin, colistin, and anidulafungin. Transfusions of blood and fresh frozen plasma along with fibrinogen replacement therapy and aggressive management of the severe haemophagocytic lymphohistiocytosis (high fever, hepatosplenomegaly, cytopenias, extremely high ferritin, low fibrinogen, haemophagocytic syndrome score (HScore) on day 1: 210 and on day 4 with additional hypertriglyceridemia: 254) with intravenous pulse infusions of 1 g methylprednisolone followed by 1 mg/kg/day of prednisolone and intravenous γ-immunoglobulin (0.4 g/kg/day for 5 days) were also given according to our experience[5-7].

On the third day, despite aggressive supportive measures, the patient was transferred to the Intensive Care Unit, where he developed multi-organ failure, diffuse lung and gastrointestinal haemorrhage and died five days later. Of note, all blood and urine cultures, and serology

	Day 1 (admission)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7 (death)
Hb (g/dl)	**10**	**9.2**	**7.7**	**5.8**	**8.2**	**8.7**	**8.6**
WBC (/µl)	6700	5000	4800	9000	5300	**3100**	**2200**
PLTs (/µl)	**20000**	**7000**	**6000**	**33000**	**68000**	**81000**	**39000**
INR (ULN: 1.15)	**1.84**	**2.23**	**2.16**	**2.38**	**2.41**	**3.25**	NA
aPTT (ULN: 36 sec)	**49**	**81**	**73**	**67**	**69**	**65**	NA
Triglycerides (ULN: 150 mg/dl)	98	96	92	**188**	**286**	**445**	**963**
Fibrinogen (180-400 mg/dl)	NA	**83**	**120**	**68**	**65**	NA	NA
Ferritin (ULN: 400 ng/ml)	**26791**	**89900**	**105707**	**98390**	**162820**	**162420**	**141560**
Urea (ULN: 48 mg/dl)	**112**	**154**	**208**	**92**	**51**	30	16
Creatinine (ULN: 1.2 mg/dl)	**2.23**	**3.46**	**4.9**	**2.73**	**1.92**	**1.77**	**1.75**
LDH (ULN: 224 U/l)	**895**	**2455**	**3951**	**7352**	**21792**	**19106**	**16177**
AST (ULN: 40 U/l)	**280**	**938**	**2384**	**5928**	**23090**	**21229**	**17453**
ALT (ULN: 40 U/l)	**87**	**269**	**775**	**1638**	**5046**	**3802**	**2438**
γ-GT (ULN: 61 U/l)	**126**	**181**	**200**	**111**	**110**	**142**	**154**
ALP (ULN: 130 U/l)	**97**	**170**	**223**	**221**	**296**	**336**	**449**
Total bilirubin (ULN: 1.2 mg/dl)	0.7	0.85	1.88	2.16	2.42	3.1	3.75

Table 1. *Case 1: Laboratory work-up (adapted from[9]).*
Abbreviations: Hb, haemoglobin; WBC, white blood cells, PLTs, platelets, INR, international normalized ratio; aPTT, activated partial thromboplastin time; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT; gamma-glutamyl transferase; ALP, alkaline phosphatase; NA not available; ULN, upper limit of normal.

investigations for Brucella, Leishmania, Leptospira, and Hantavirus tested negative. On day 7 of admission (death date), CCHF virus was detected by reverse transcription polymerase chain reaction in his blood sample at the National Reference Centre for Arboviruses and Hemorrhagic Fever viruses (Department of Microbiology, Medical School of Aristotle University, Thessaloniki, Greece).

On the day the patient died, a 54-year-old female internist, who was on duty at his admission, with no remarkable medical history, reported fever (38.5°C), myalgias and sore throat. Laboratory investigation showed leukopenia, thrombocytopenia, and elevated lactate dehydrogenase, D-dimers, triglycerides and ferritin *(Table 2)*. Due to the recent contact with the index patient without personal protective equipment, she was immediately investigated for CCHF virus infection, proved to be positive. She was immediately treated with oral ribavirin (30 mg/kg po initial dose, then 15 mg/kg q6h ×4 days, then 7.5 mg/kg q8h po ×6 days according to the World Health Organization recommendation[8]), along with one pulse intravenous infusion of 500 mg methylprednisolone followed by 1 mg/kg/day of prednisolone with appropriate rapid tapering and γ-globulins for 5 days, as potential early stage haemophagocytic lymphohistiocytosis (HScore on day 1 to 3: 150). She gradually improved during the following days, and she was discharged on day 7, with full recovery.

As our study was not interventional, approval from our local ethical committee was not required. Written informed consents were obtained from the second case and the first patient's family.

DISCUSSION

CCHF is a severe but not endemic disease in Greece, as so far only one autochthonous case has been reported[2]. It is a tick-borne disease, which is transmitted mainly by bites of Hyalomma ticks (the main vector) or through direct contact with blood and/or biological fluids of affected patients and animals[1,2]. From the epidemiological and preventive perspectives, the precise and detailed epidemiological, epi-zootiological and environmental investigations along with outbreak control measures including infection prevention and contact management concerning these two cases have been published recently[9].

In the first case the disease course marked rapid progression to severe and finally fatal haemophagocytic lymphohistiocytosis. Central nervous system involvement,

	Day 1 (admission)	Day 3	Day 4	Day 5	Day 7 (discharge)
Hb (g/dl)	12.2	**11.9**	12.4	12.1	**11**
WBC (/µl)	**1500**	4300	**3900**	**3400**	4800
PLTs (/µl)	80000	110000	105000	140000	175000
INR (ULN: 1.15)	0.98	0.76	0.73	0.82	0.86
aPTT (ULN: 36 sec)	**37**	28	26	25	22
D-dimer (ULN: 243 ng/ml)	**1250**	**697**	**739**	**795**	**551**
Triglycerides (ULN: 150 mg/dl)	**170**	**197**	**205**	140	135
Fibrinogen (180-400 mg/dl)	290	237	216	220	223
Ferritin (ULN: 400 ng/ml)	**1077**	**762**	**692**	**819**	**989**
Urea (ULN: 48 mg/dl)	28	28	28	34	40
Creatinine (ULN: 1.2 mg/dl)	1.02	0.87	0.87	0.84	0.8
LDH (ULN: 224 U/l)	**310**	**287**	**292**	**293**	**308**
AST (ULN: 40 U/l)	**48**	38	**54**	**65**	**45**
ALT (ULN: 40 U/l)	21	20	33	**46**	**42**
γ-GT (ULN: 61 U/l)	22	33	**62**	**83**	**90**
ALP (ULN: 130 U/l)	94	71	72	72	73
Total bilirubin (ULN: 1.2 mg/dl)	0.38	0.44	0.69	**1.44**	**1.8**

Table 2. *Case 2: Laboratory work-up (adapted from[9]).*
Abbreviations: Hb, haemoglobin; WBC, white blood cells, PLTs, platelets, INR, international normalized ratio; aPTT, activated partial thromboplastin time; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GT; gamma-glutamyl transferase; ALP, alkaline phosphatase; NA not available; ULN, upper limit of normal.

liver failure, multiple-organ dysfunction, and particularly, higher baseline ferritin levels along with failure of ferritin to improve during therapy, are associated with a poor prognosis[3]. Infections have an important role in the aetiology of haemophagocytic lymphohistiocytosis, as it has been associated with many viral, bacterial, fungal, and parasitic infections[3,4]. Among them Epstein-Barr virus is the commonest triggering agent but human herpesvirus 8, cytomegalovirus, influenza virus, parvovirus, hepatitis viruses, enterovirus, bacteria including mycobacteria, parasites and spirochaetes have also been described[4]. In this context, CCHF virus has rarely been identified as the causative agent of severe haemophagocytic lymphohistiocytosis. Indeed, up to the present, only few cases of haemophagocytic lymphohistiocytosis, all from Turkey, have been reported in patients with established CCHF[10,11].

Diagnosis of secondary haemophagocytic lymphohistiocytosis in adults is usually challenging because of limited awareness and difficulties with diagnosis in view of contested clinical criteria. Indeed, the hyperinflammatory spectrum in haemophagocytic lymphohistiocytosis varies from an indolent state to a severe, fulminant and potentially fatal situation, with non-specific overlapping features of many systemic illnesses, including the potential underlying drivers themselves. Diagnostic criteria have already been developed for adults with malignancy or infection-related secondary haemophagocytic lymphohistiocytosis with good sensitivity and specificity (HScore; sensitivity 90%; specificity 86%), even though the HScore is insufficient to diagnose haemophagocytic lymphohistiocytosis across all settings and populations. In this context, hyperferritinemia is a key laboratory feature, as both peak ferritin and a decrease of less than 50% after treatment are associated with a poor outcome. If ferritin is normal but there is ongoing clinical suspicion for haemophagocytic lymphohistiocytosis, serial ferritin testing should be performed.

Early identification and intervention are crucial for the patients, as they can prevent organ failure and death. Unfortunately, in adults, the diagnostic criteria are usually strictly fulfilled only in the advanced stages when starting treatment might already be ineffective (as in our first case). Therefore, in general, withholding potentially life-saving

therapy until criteria are met could result in a missed window of opportunity before rapid clinical deterioration leading to irreversible decline. Therefore, we accelerated management in the second patient even though the HScore was high normal (borderline), with a ferritin level that was abnormal but less than 2000 ng/ml.

Initial empiric immunomodulatory treatment in patients with rapidly progressive haemophagocytic lymphohistiocytosis usually includes high-dose corticosteroids, anakinra (interleukin-1 receptor antagonist) and/or γ-globulins often in combination[3]. Even though the use of corticosteroids could mask underlying lymphoma, it is exceptionally difficult to achieve response in patients with severe haemophagocytic lymphohistiocytosis with a steroid-free regimen during the induction phase. Treatment should be started as soon as there is sufficient clinical suspicion of haemophagocytic lymphohistiocytosis, ideally within 12h. In parallel, a thorough work-up should immediately start against underlying infections, autoimmune rheumatic diseases, or malignancies. Treatment should not be withheld until the identification of the causative trigger, but specific additional therapy is commonly needed if the trigger is identified to tackle the primary cause of hyperinflammation. This was done in the second case where prompt and timely initiation of ribavirin (to stop the active viral replication) along with immunomodulation (steroids plus γ-globulins to tackle early stage haemophagocytic lymphohistiocytosis) led to full recovery, highlighting the value of rapid recognition and treatment.

CONCLUSIONS

Secondary haemophagocytic lymphohistiocytosis can rapidly lead to serious illness and death if not diagnosed and managed promptly. Therefore, clinical suspicion should be high, particularly in cases with unexplained fever and cytopenias accompanied by very high ferritin and hypertriglyceridemia or low fibrinogen. In infectious-related haemophagocytic lymphohistiocytosis, dual therapeutic strategies should be started as soon as possible against the causative agent and haemophagocytic lymphohistiocytosis itself even in cases without strict confirmation of its criteria, as prompt initiation of treatment at early stages can be lifesaving. In this context, our cases emphasize that CCHF virus can be a cause of severe life-threatening secondary haemophagocytic lymphohistiocytosis even in non-endemic areas, while stringent infection control to prevent secondary healthcare-associated transmissions is of the utmost importance.

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