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CASE REPORT

Infection-triggered haemophagocytic lymphohistiocytosis

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Abstract
Haemophagocytic lymphohistiocytosis (HLH) is an under-recognised syndrome. We present a case of a Somalian male with haemophagocytic lymphohistiocytosis triggered by Epstein-Barr virus and *Mycobacterium tuberculosis*. HLH can be triggered by many different acute primary infections or by reactivation of chronic infections. Lessons learned from this case include the value of awareness of HLH including the criteria, symptoms and triggers of this syndrome.

Introduction
Haemophagocytic lymphohistiocytosis (HLH) is a life-threatening epiphenomenon with a wide range of causes in all age groups.[1] It is a syndrome caused by uncontrolled immune activation with a non-specific clinical presentation and can lead to critically ill patients.[1,2] Most infectious triggers of HLH are common viral infections, but relatively uncommon mycobacterial infections in the Netherlands can trigger HLH as well.[3]
We describe a case of HLH associated with Epstein-Barr virus (EBV) and *Mycobacterium tuberculosis*.

Case presentation
A 48-year-old Somalian male (immigrated 25 years earlier to the Netherlands at age 23) was admitted to the ward with fever, tachypnoea and general deterioration. Pneumonia was suspected for which amoxicillin was started. Two days later the

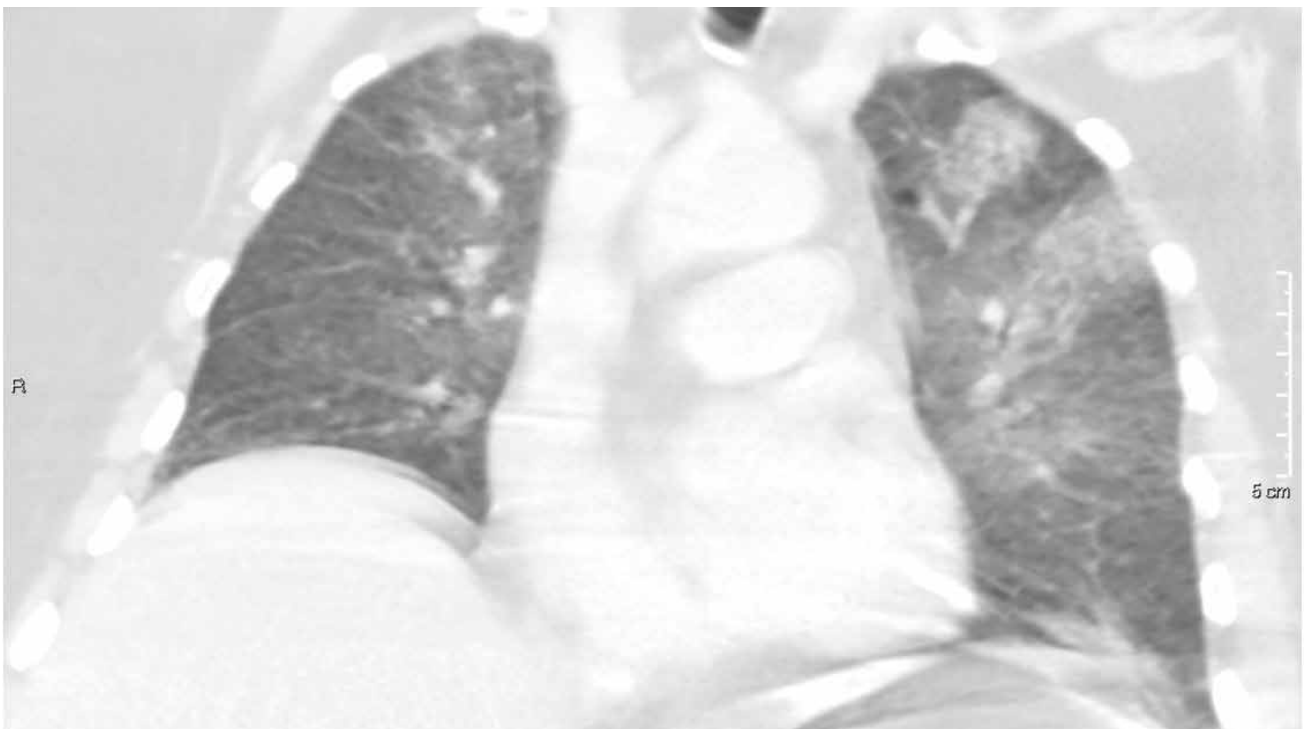

Figure 1. Computer tomographic examination of chest

patient was admitted to the ICU due to further deterioration. His heart rate was 150 beats/min and irregular, blood pressure 104/56 mmHg and temperature 39˚C. Striking was the rapid superficial respiratory rate of up to 60/min, saturation 90% with 6 litres of oxygen. Vesicular breathing sounds were heard with expiratory wheezing. Further physical examination was unremarkable. Laboratory evaluations revealed a C-reactive protein of 123 mg/l, procalcitonin 1.5 ng/ml, haemoglobin 8.0 mmol/l, total leucocyte count 6.1 x 10^9/l, neutrophil count 5.39 x 10^9/l, platelet count 14 x 10^9/l, lymphocytes 0.47 x 10^9/l, creatinine 81 μmol/l, bilirubin 24 μmol/l, ASAT 195 U/l, ALAT 75 U/l, gamma-GT 259 U/l, and alkaline phosphatase 88 U/l. Urine antigen tests were negative for *Legionella pneumophila* and *Streptococcus pneumonia*. Computer tomographic examination of chest and abdomen showed low-density consolidations of both upper lobes, no lymphadenopathy and no intra-abdominal abnormalities *(figure 1)*. Amoxicillin was switched to cefuroxime and together with high-flow nasal oxygen therapy the patient seemed to improve. Yet, after one week, intubation was necessary due to sudden respiratory failure. Broncho-alveolar lavage (BAL) demonstrated *Candida albicans*; other routine cultures as well as polymerase chain reactions (PCR) for atypical microorganisms and tuberculosis (TB) were negative, as was auramine staining. During the following week the patient developed kidney failure (creatinine 247 μmol/l), pancytopenia (haemoglobin 4.8 mmol/l, total leucocyte count 2.8 x 10^9/l, platelet count 20 x 10^9/l, lymphocytes 3.2%), disseminated intravascular coagulation (APTT 49.5 sec, PT 13.6, fibrinogen 1.9 g/l), haematochezia and deteriorating liver enzymes values (bilirubin 133 μmol/l, ASAT 192 U/l, ALAT 99 U/l, gamma-GT 917 U/l, alkaline phosphatase 244 U/l). Blood cultures included *Staphylococcus haemolyticus* but further blood cultures remained negative after treatment with vancomycin. BAL was repeated after intubation, but routine cultures and PCR for atypical microorganisms and TB remained negative. Microbiological testing disclosed a chronic hepatitis B virus infection and EBV reactivation with a high viral load. Furthermore, human immunodeficiency virus, cytomegalovirus, varicella and leishmania tested negative. The combination of pancytopenia and EBV reactivation led to the suspicion of HLH *(table 1)*. Ferritin levels were strikingly elevated and the bone marrow biopsy demonstrated marked erythrophagocytosis; Ziehl-Neelsen colouring and auramine staining were negative. The diagnosis of HLH was established with EBV as suspected trigger. Treatment with dexamethasone, intravenous immunoglobulin and rituximab was started. Nevertheless, the patient's condition deteriorated due to progressive multi-organ failure and he died two days after starting treatment for HLH. Autopsy demonstrated extensive necrotising granulomatous inflammation in the lungs, liver, spleen, lymph nodes and bone marrow with a positive acid-fast Ziehl-Neelsen colouring, suspect for mycobacteria. Post mortem, eight weeks after obtaining bronchoalveolar lavage fluid, the culture showed growth of *M. tuberculosis*.

Discussion

Reactive HLH is a life-threatening syndrome based on uncontrolled immune activation triggered by infection, autoimmune disease or malignancy.[2] It is characterised by defective cytotoxic cell function combined with unbridled macrophage activity leading to excessive production of cytokines. This leads to immune dysregulation and tissue damage.[1,4,5] It can be difficult to diagnose because it presents as a normal infection with a non-specific clinical presentation. Symptoms are prolonged fever, hepatosplenomegaly and cytopenia. Hyperferritinaemia, hypertriglyceridemia, low natural killer cell activity, increased soluble CD-25 levels and liver dysfunction are all characteristic for HLH.[1,2,4-6]

The most common triggers of HLH are viral or mycobacterial infections. Viral infection can cause HLH, especially acute or reactivation of chronic herpes viruses such as EBV and cytomegalovirus. The same virus can either act as an acute trigger of HLH in healthy persons or as the underlying predisposing disease during a chronic infection in immunosuppressed persons.[1,2,4-5] Bacterial infections are less common triggers.[2,7] A combination of two or three infections in patients with HLH is also described as trigger, although this mainly occurs in HIV-infected or immune-compromised patients.[7]

HLH treatment is focused on supportive care, elimination of the trigger and suppression of the inflammatory response.[1,2,4-6] EBV-associated HLH without early therapy has a high mortality rate. A few small studies have showed potential benefit of etoposide and rituximab treatment for EBV-associated HLH.[2] Treatment according to the HLH guidelines demonstrates a

Table 1. Haemophagocytic lymphohistiocytosis criteria.

Haemophagocytic lymphohistiocytosis criteria	Case	Condition met
Fever ≥38.5°C	39.3°C	Yes (1)
Splenomegaly	No	No
Cytopenias (affecting at least two of three cell lineages in the peripheral blood): Haemoglobin <5.59 mmol/l Platelets <100 cells per 10^9/l Neutrophils <1 cell per 10^9/l	Haemoglobin 4.8 mmol/l Platelets 20 10E9/l Leucocyte count 2.8 10E9/l	Yes (2)
Hypertriglyceridaemia (fasting, >3 mmol/l) and hypofibrinogenaemia (<1.7 mmol/l)	Triglycerides 2.64 mmol/l Fibrinogen 1.9 g/l	No
Haemophagocytosis in bone marrow, spleen, lymph nodes, or liver	In bone marrow	Yes (3)
Low or absent natural killer-cell activity	NK-cell 0.01 10E6/ml	Yes (4)
Ferritin greater than 1123.5 pmol/l	Ferritin 6856 μg/l	Yes (5)
Increased soluble CD25 concentration (alpha chain of soluble interleukin 2 receptor)	IL-2 10910 U/ml	Yes (6)

Five of the eight findings are necessary for diagnosing HLH.

significant advantage in cases in which the underlying trigger is treated.[2] However, our patient had too far advanced multi-organ failure for etoposide treatment.

M. tuberculosis is the most common mycobacterial trigger of HLH.[2,7] Standard diagnostic tests for patients who are suspected of TB include a chest X-ray, acid-fast bacilli smear and bacteriological culture tests. Mycobacterial culture has the highest sensitivity for diagnosing TB, but it can take weeks to months. Sputum smear microscopy is rapid and simple for diagnosing TB, but it has a low and variable sensitivity.[8] PCR-TB testing of the two bronchoalveolar lavage fluids of the lungs and the bone marrow aspirate obtained during life were negative. Cultures of gastric aspirate were not sampled because of limited effectiveness due to lower sensitivity in comparison to BAL.[14] In general, the sensitivity and specificity of PCR is 93% and 84% respectively in countries with a high incidence of TB.[15] The post-mortem diagnosis of TB by positive cultures for M. tuberculosis demonstrates the limitation of the PCR technique to detect TB infections.

Conclusion

Our patient died due to HLH associated with EBV and M. tuberculosis. HLH can be triggered by many different acute primary infections or by reactivation of a chronic infection. Lessons learned from this case include valuing knowledge of HLH such as criteria, symptoms and triggers of this particular syndrome. In addition, this case also demonstrated the pitfalls of even the most modern diagnostic modalities to diagnose TB.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

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Erratum

In: van der Voort PHJ, Buitinck S, Jansen RR, Franssen EJF, Determann RM. Ten tips and tricks for successful digestive tract decontamination. Neth J Crit Care. 2019;27:87-90 a typing error was noticed.

Under tip & trick number 7, "A 100 ml solution containing 50 mg of amphotericin B can be instilled twice daily and left in the bladder for one hour." should be replaced by "A 100 ml solution containing 5 mg of amphotericin B can be instilled twice daily and left in the bladder for one hour."

It may be important for you to know that when 50 mg instead of 5 mg is instilled, no side effects are expected.