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SOLVING CLINICAL PROBLEMS IN BLOOD DISEASES

Cloak and dagger - secondary hemophygocytic lymphohistiocytosis caused by intravenous autoinfection

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1 | CASE PRESENTATION

We herein report on a 28-year-old, Caucasian, female patient presenting with high fever spurts and abdominal pain. After intensive work-up and exclusion of common differential diagnosis, the working diagnosis was fever of unknown origin (FUO). Blood cultures positive for unusual fecal bacteria led to the suspicion of a secondary hemophagocytic lymphohistiocytosis (sHLH) upon repeated autoinfection with feces due to an underlying psychiatric disease.

The patient presented to the emergency department due to acute abdominal pain and a history of fever spurts. Initial physical examination and laboratory tests revealed a cardiopulmonary and abdominal status without pathological findings. From her past medical history, the patient reported juvenile idiopathic arthritis (low disease activity), ulcerative colitis (in remission) and an acute pancreatitis 2 years ago. Based on the clinical presentation and past medical history, the initial differential diagnosis included among others acute pancreatitis, nephrolithiasis, and cholecystitis.

Initial laboratory analyses revealed elevated transaminases and alkaline phosphatase with ALT 90 U/L (reference range 10-50 U/L), AST 95 U/L (10-50 U/L), gamma-GT 199 U/L (6-42 U/L), AP 299 U/L (35-105 U/L), increased lipase activity 796 U/L (13-60 U/L) and a significantly increased C-reactive protein (CRP) of 10.64 mg/dL (<0.5 mg/dL). The blood count showed hemoglobin, leukocytes and thrombocytes within normal ranges. Abdominal sonography and magnetic resonance imaging (MRI) showed signs of pancreatitis as well as a splenomegaly (20 cm) but no evidence of acute cholecystitis or nephrolithiasis was found. Subsequently, the diagnosis acute pancreatitis was made.

Consecutively, fluid replacement, analgesics and antibiotics were initiated, causing pain reduction and normalization in lipase. However, before discharge, fever recurred (up to 41.3°C) accompanied by severe pain, chills, tachycardia and erysipelas, around a peripherally inserted venous catheter on the patient's forearm (Figure 1A). Despite multiple adaptations of the antibiotic therapy, recurrent fever episodes persisted (Figure 1B). In the light of her past medical history, adult onset Still's disease was suspected, and treatment with anakinra (4 x 100 mg per day) was commenced. However, treatment with this interleukin-1 inhibitor was unsuccessful and fever episodes persisted.

After exclusion of endocarditis by trans-esophageal echocardiography and exclusion of tuberculosis, her fever persisted and the diagnosis fever of unknown origin (FUO) was made. Due to a newly developed bicytopenia (leukopenia and anemia), a bone marrow aspirate was performed, showing hyperplasia of the myeloid linage with depressed erythropoiesis, increased megakaryocytes and macrophages with hemophagocytosis (Figure 2).

Worsening anemia and thrombocytopenia, as well as hypertriglyceridemia (263 mg/dL), hypofibrinogenemia (176 mg/dL) and elevated s-IL2 R (>20 ng/mL) are suggestive for sHLH. Together with pyrexia, splenomegaly, hemophagocytosis, and elevated GOT, those

Andreas Pircher and Stefan Koeck contributed equally to this work.

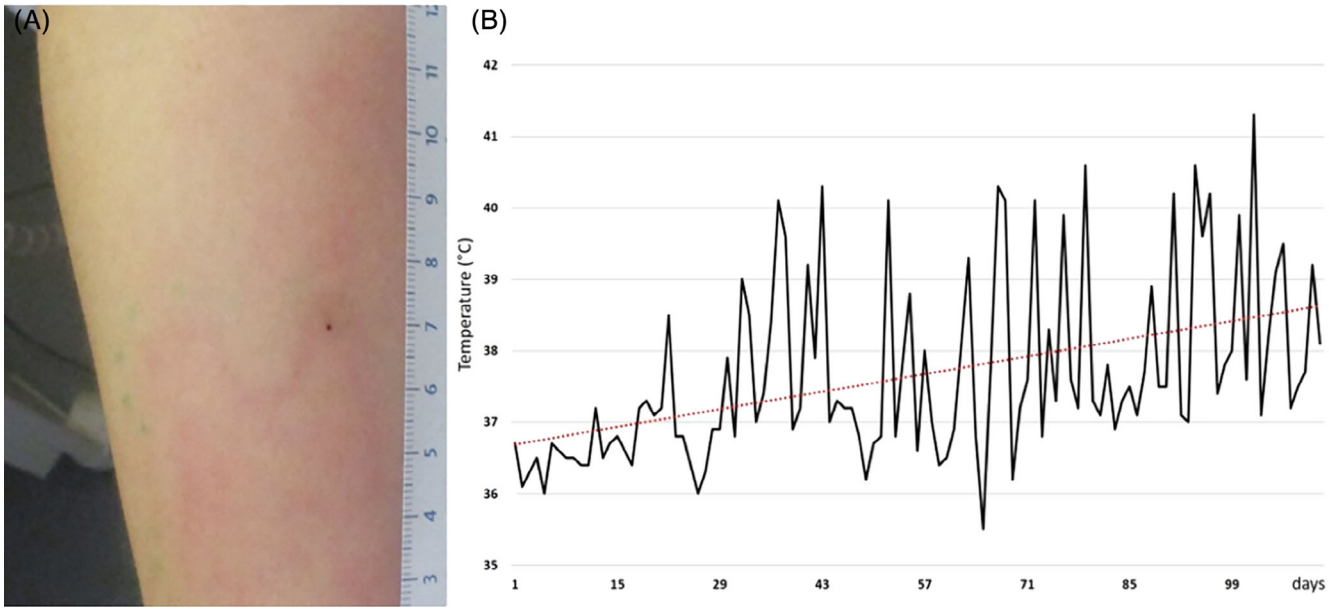

FIGURE 1 A, Photograph of the patients forearm showing an example of the cutaneous inflammation of the puncture site, which led to removal of the peripheral venous catheter. B, Recordings of the patient's body temperature during hospitalization showing recurrent high fever episodes

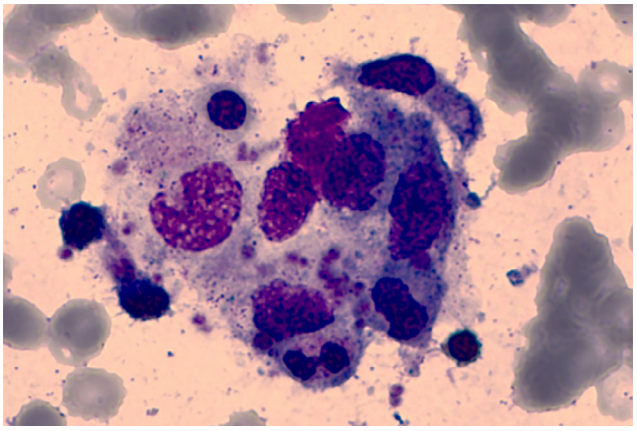

FIGURE 2 Representative image from bone marrow cytology, showing an activated macrophage in the process of phagocytosis of multiple precursor cells of the erythrocyte lineage

findings predicted HLH with a 98.4% probability in the H-score.[1] She thus fulfilled six out of eight HLH-2004 criteria which are required for the diagnosis of HLH.[2]

The current development of sHLH was interpreted as secondary to infection. Fever episodes correlated well with an increase in CRP and pro-calcitonin levels (up to 13.17 mg/dL and 84.20 μg/L respectively). Repeated blood cultures revealed bacteremia with different germs (*Enterococcus faecium*, *Lactobacillus rhamnosus*, *Micrococcus luteus*, *Clostridium paraputrificum*, *Escherichia coli*).

Because of sHLH caused by bacteremia with an unusual fecal bacterial spectrum and recurrent inflammation of peripheral venous catheter insertion sites, artificial autoinfection with feces, attributed to a newly diagnosed Munchhausen syndrome,[3] was suspected. Actually, Munchhausen syndrome was verified by consultation of psychiatrists and the discovery of feces-filled syringes in the patient's room. When all catheters (which apparently served as injection route) were removed, symptoms disappeared under oral antibiotic therapy within a short period of time. No continuation therapy of any kind was administered and no relapse was recorded during a follow up time of 14 months.

2 | DISCUSSION

Here we report for the first time the association of repeated autoinfection with feces and the development of sHLH. Note, HLH is a life threatening hyperinflammatory syndrome. Originally, it was discovered in 1952 and characterized as a cytopenia syndrome of unknown origin with concomitant lymphocytic infiltrates and benign histiocytosis.[4] Today it is understood that HLH evolves out of a greatly stimulated but overly inefficient immune response, and is characterized by continuously high fever, cytopenia, hyperferritinemia and hemophagocytosis.[5,6] Traditionally it is classified as genetic primary or familial HLH (fHLH), usually appearing in infancy or childhood, and acquired secondary HLH (sHLH) appearing later in life. Without treatment it is almost universally fatal.[7] And, sHLH has been associated with a variety of viral, bacterial, fungal, and parasitic infections as well as malignancies.[8] Repeated autoinoculation with feces represents another, so far unknown cause of sHLH. Supporting evidence for this notion derives from animal studies by Behrens et al. who showed that wild-type mice developed sHLH features, upon repeated administration of DNA fragments containing CpG sequences, which are a known TLR9 ligands.[9] The authors propose that TLR activation by danger-

associated molecular patterns (DAMP), in the case of high viral load in EBV-HLH, or DAMP such as self DNA/RNA fragments in autoimmune diseases such as SLE, may lead to the cytokine storm syndrome. Moreover, recent data suggest that the exposition to TLR agonists lead to sHLH by modulating the transcriptome of macrophages.[10]

Regarding the current case, *Enterococcus faecium* and *Escherichia coli* are commonly known to be obligate pathogens after invasion into the blood stream, whereas *Lactobacillus rhamnosus*, *Micrococcus luteus* and *Clostridium paraputrificum* are part of the physiological intestinal microbiota, causing manifest systemic infections only under severe immunodeficiency.[11,12]

Interestingly, the majority of gram-negative bacteremia do not induce sHLH. Two special conditions in this case might lead to the development of hyperinflammation. First, the rapid appearance of physiological intestinal microbiota in the blood stream, which are normally not recognizable by the immune system, can lead to an uncontrolled systemic response. Second, a pre-existing autoimmune disease in form of the juvenile idiopathic arthritis might increase the susceptibility for HLH.

In contrast to the animal experiment, our patient did not develop hyperferritinemia, a classical pathognomic marker for the presence of HLH, but she fulfilled all other criteria of HLH (NK cell activity was not measured), especially cytologically proven hemophagocytosis in the bone marrow (Figure 2). Experimentally, hemophagocytosis was only found in TLR-9 stimulated mice when anti-IL10R was administered additionally.[9] This highlights the immunoregulatory role of IL-10 and a dysregulated immune response as the underlying mechanism in the evolution of HLH.[2,13] Moreover, IL-10 plays a crucial role in the pathophysiology of rheumatoid diseases.[14] These data support our theory that in this case the pre-existing juvenile idiopathic arthritis might increase the susceptibility for HLH in the presence of a gram-negative bacteremia. HLH develops secondary to differently strong immunologic triggers on the background of individual genetic susceptibility to hyperinflammation.[15]

In conclusion, this case shows that repeated intravenous injection of fecal microbes caused by an underlying psychiatric disease can trigger a hyper-activated immune response inducing HLH. Muenchhausen syndrome should therefore be considered as a differential diagnosis in patients with unexplained and recurrent sHLH. Just like in a classical "cloak and dagger operation" this case highlights how the immune system's contact with fecal microbiota uncovered a psychiatric disease. Interestingly, the presented cause of repeated autoinoculation with feces causing the development of sHLH has not been previously reported in literature.

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