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Hemophagocytic lymphohistiocytosis in a patient with Sjögren's syndrome: case report and review

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Abstract Hemophagocytic lymphohistiocytosis (HLH) is a very rare syndrome with a mortality up to 95% of cases if not treated. It is characterised by an excessive activation of the immune system that leads to a disproportionate and destructive inflammatory response. The high mortality rates are in part due to a delay in the diagnosis, and therefore clinicians must maintain a high index of suspicion. When the treatment is started early, the survival rate reaches around 55% of cases. HLH usually presents with persistent fever, pancytopenia, and organomegaly and is associated with very high levels of serum ferritin. In this manuscript, we present the case of a patient with primary Sjögren's syndrome who developed HLH after an acute infection by Cytomegalovirus. We will describe and discuss the pathogenesis, differential diagnosis and a pragmatic approach to the treatment for this critically important and, when diagnosed early, potentially curable syndrome.

Keywords Hemophagocytic lymphohistiocytosis · HLH · Sjögren's syndrome · *Cytomegalovirus* · CMV

Case report

A 70-year-old woman was admitted to the emergency department presenting with a fever of 39 °C, asthenia, a dry cough and rapid weight loss of 2 kg within 12 days. Her previous medical history consisted of systemic hypertension controlled with valsartan.

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The physical examination (including cardiorespiratory, gastrointestinal, lymph nodes and ear, nose and throat) did not reveal any abnormalities. Initial laboratory studies revealed leukocytosis, thrombocytopenia, hypertransaminasemia and hypertriglyceridemia in addition to elevated lactate dehydrogenase (LDH), serum ferritin, uricemia and C reactive protein (CRP) levels. The chest radiograph was normal with no focal abnormality. The urinalysis was normal with no active renal sediment.

The patient was hospitalized with a clinical diagnosis of an atypical lower respiratory infection. Blood cultures were extracted, and she was commenced on levofloxacin 500 mg intravenous (i/v) every 24 h. Despite several days of treatment, her fever persisted with no specific pattern and no rash was observed. Laboratory tests worsened with the development of normocytic normochromic anemia, low serum fibrinogen and a deterioration of renal function. Fibrinogen 1 g every 12 h had to be administered. Serological tests were performed in order to rule out infection by atypical bacteria or viruses [*Brucella, Coxiella, Mycobacterium tuberculosis, Mycobacterium avium, Borrelia, Leishmania, hepatitis A, B and C (VHA, VHB, VHC), human immunodeficiency virus (HIV), Cytomegalovirus (CMV) and Epstein–Barr Virus (EBV)*].

The chest, abdomen and pelvic computer tomography (CT) scans and the abdominal ultrasound (US) revealed mild hepatosplenomegaly in the absence of swollen lymph nodes or tumor.

The rheumatology department requested a complete immunology assessment when the patient reported a history of several years of eye and mouth dryness. Adult Still's disease and HLH were also considered in the differential diagnosis due to high levels of ferritin (58,300 ng/mL) although the patient did not disclose a history of arthralgias or skin rash. The hematology department performed

Table 1 Blood parameters

	At arrival	1 Week after admission	After treatment	Reference value
Hemoglobin	12.2	10.7	13.3	12–16 g/dL
Platelets	107,000	77,000	184,000	140,000–400,000 IU/μL
Leukocytes	13,800	7500	9500	4000–10,000 IU/μL
ALT	99	115	19	5–31 IU/L
AST	64	145	27	10–31 IU/L
GGT	37	96	12	6–40 IU/L
LDH		578	176	135–214 IU/L
Alkaline phosphatase	91	140	68	35–105 IU/L
Triglycerides	225	259	124	50–150 mg/dL
Fibrinogen	273	56	213	150–450 mg/dL
C reactive protein	2.3	24.4	0.5	0–0.5 mg/dL
Ferritin		58,281	135	12–200 μg/L
Uric acid	9.8		5.2	2.4–6 mg/dL
Creatinine	1.34	1.71	0.72	0.5–0.9 mg/dL
Glomerular filtration	39	29	>60	>60 mL/min/1.73 m^2

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *GGT* gamma glutamyl transferase, *LDH* lactate dehydrogenase
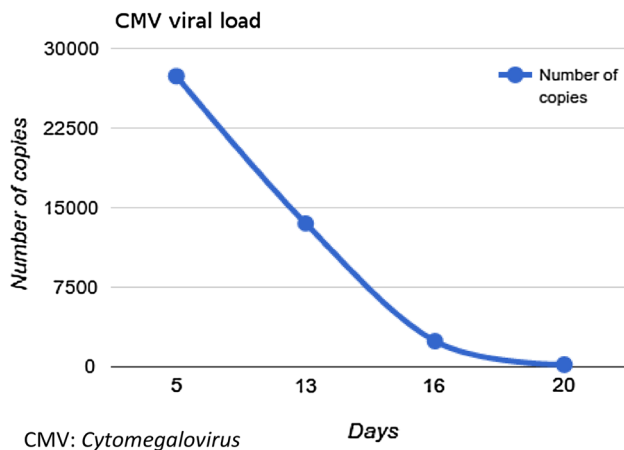

Fig. 1 Evolution of the viral load once the treatment was started. *CMV* cytomegalovirus

a bone marrow biopsy which revealed hemophagocytosis, plasmacytosis and no signs of malignancy, findings consistent with HLH. The serology and microbiology tests were negative for all the previously described infectious agents, except for elevated CMV immunoglobulin M (IgM) antibodies and a viral load of 27,400 copies.

The final diagnosis was HLH triggered by an acute CMV infection, and intravenous (IV) ganciclovir (5 mg/kg/day) was started on the 10th day of hospitalization. After 2 weeks of treatment, the patient felt better and every altered parameter had normalized (Table 1). The viral load decreased to 2300 copies (Fig. 1). When the microbiology department considered that the infection was controlled, immunosuppressive treatment with i/v methylprednisolone

500 mg/day was administered for 3 days, followed by cyclosporine 6 mg/kg/day.

The patient was discharged from the hospital 4 weeks after admission. Immunology tests performed at admission were positive for anti-Ro and anti-La antibodies. A salivary glands gammagraphy, Schirmer's test and a biopsy of the salivary glands confirmed the suspicion of pSS and treatment was initiated with hydroxychloroquine 200 mg every 12 h orally and saline eye drops. The rest of the immunologic assessment was negative, including genetic mutations.

We describe the main primary autoimmune conditions (including pSS) and a number of infectious agents (including *CMV*) that are recognized causes of HLH. However, there seems to be an underlying alteration in the immunity (might be identified or not) that is always working as the predisposing factor.

Discussion

HLH is a life-threatening condition consisting of an excessive immune activation. It is essential to consider this diagnosis because the mortality rate can be up to 95% without treatment, and a delay also worsens the prognosis, as the median survival time without treatment is 2 months [1]. It was first described in 1939 but the knowledge about this syndrome is still quite limited due to the small sample size of patients, which makes a study extremely challenging [2]. It presents in patients of all ages, more commonly in children. No data are available concerning its global prevalence. Primary forms of HLH usually appear within the first 3 months of life, and it is equally present in both genders

[3]. In the adult population, it is slightly more common in males [4].

The underlying cause of this syndrome is an alteration of the perforin-dependent cytotoxicity [5]. It can consist of one single episode or be a relapsing disease. There is an excessive secretion of cytokines by macrophages (cytokine storm) and an impairment of the natural killer (NK) cells. On the other hand, macrophages literally "eat" blood cells. This process can be observed in the bone marrow (as in our patient) lymph nodes, spleen and liver biopsies [6–8].

There are two *forms of primary HLH*: Familial hemophagocytic lymphohistiocytosis, which tends to present at a young age (70 % in children under 1 year old and 14 % in adults) [9–12] and genetic immunodeficiency syndromes [i.e., Griscelli Sd, Chediak–Higashi and Hermansky–Pudlak syndromes, XMEN ("X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia"), X-linked lymphoproliferative and chronic granulomatous diseases] [13–18].

Sepulveda et al. [19] carried out an observational study with mice and suggested that primary inherited forms of HLH could be caused by bi-allelic mutations in genes coding perforin-dependent cytotoxicity.

Secondary forms of HLH are associated with infections, malignancies (essentially lymphoma, leukemia and myelodysplasia) [20, 21], acquired immunodeficiency and macrophage activation syndrome (MAS). When infections are involved, the trigger is usually a microorganism with an intracellular replicative cycle and systemic bacteria. Our patient was infected by CMV, but other viral triggers have been described such as *EBV, HIV, VHA, VHB, VCH, human perpesvirus, varicella zoster, herpes simplex, influenza* and *parainfluenza* and *measles virus.* Some examples of bacterial etiologies are *mycobacteria, Brucella, Rickettsia, Hemophilus influenzae* and *Serratia* sp. The most common parasites are *Leishmania* and *Toxoplasma* [22–30].

Sepulveda et al. [19] also reported that a small number of patients with a secondary form of HLH were carriers of a monoallelic mutation of one or more genes associated with HLH; however, the results pointed toward a polygenic inheritance.

Macrophage activation syndrome is considered to be a special form of secondary HLH that occurs in patients with an underlying autoimmune disease. It is also known as "reactive hemophagocytic syndrome" and has a mortality rate of up to 50% [31]. Of all HLH cases, 5% present as such and our patient was one of those. The debut of a systemic disease might be the only underlying cause in developing HLH. However, some rheumatic diseases only play a role as a predisposing factor and in fact need an infection to work as a trigger [32–34]. Our patient probably suffered from Sjögren's syndrome for several years before the

diagnosis and the infection by CMV could have been the trigger.

As far as the clinical manifestations are concerned, the first and one of the most prevalent symptoms is fever, which appears in 93 % of patients as a result of high levels of interleukins. The unrelenting fever is usually what makes the patient seek medical help. No fever pattern has been identified, but body temperature can reach up to 40 °C. Splenomegaly is secondary to lymphocytic and macrophagic infiltration and appears in 96% of patients. Hepatomegaly is present in 95% of cases. Lymphadenopathy, neurological alterations and skin rashes are only found in 30% of HLH cases [35].

The lack of specificity of the clinical features is precisely what makes this syndrome so hard to diagnose. It can simulate common diseases such as hepatitis or encephalitis. The underlying genetic alteration does not cause different symptoms, except for a few exceptions, which are related to specific manifestations besides the common ones [36, 37].

Neurological involvement is quite variable and can be as mild as a headache or as severe as ataxia or a demyelinating pathology. There is also an increased risk of encephalopathy, which is reversible in most cases, consisting of headache, low consciousness and visual impairment. Patients may present hypodense or necrotic areas on a magnetic resonance imaging (MRI) and up to half of them have abnormalities in the cerebrospinal fluid (CSF) [38].

Other possible manifestations are acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), bleeding or renal dysfunction [35, 39].

Concerning the laboratory findings, cytopenias are seen in 75% of patients and can be explained by high concentrations of α-tumor necrosis factor (TNF-α) and interferon. The final platelet count is usually the most affected with an average of 70,000 U/µL. Hemoglobin can decrease as low as 3 g/dL [40]. Serum ferritin levels tend to be higher than expected for an acute phase reactant and remain between 500 and 10,000 ng/mL. Children tend to present higher concentrations (levels >10,000 ng/mL have a specificity of 95 %) in contrast to adults, whose levels usually remain around 2000 ng/mL. Older patients are also likely to suffer from other causes that can justify this elevation, such as concomitant infections, sepsis or organ failure, which makes hyperferritinemia less specific. It is important to remember that macrophages are a source of ferritin, which clearly explains the link [1, 37].

Hepatic function is altered, which often can mimic hepatitis. Transaminases are elevated as well as lactate dehydrogenase (LDH) and alkaline phosphatase (AP). High triglycerides are secondary to an increase in the levels of TNF-α and a lower activity of lipoprotein lipase. As hepatic function is impaired, hypofibrinogenemia is common and coagulation

HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis

It is necessary to have either a molecular confirmation or the presence of 5 or more of the following features:

-Fever > 38.5ºC
- Splenomegaly
 -Cytopenia of at least 2 cell types in peripheral blood: Hb<9 g/dL, platelets < 100,000 /microL, absolute neutrophil count <1,000/microL.
-Hypertriglyceridemia > 265 mg/dL and or hypofibrinogenemia < 150 mg/dL
-Hemophagocytosis in bone marrow, spleen, lymph node or liver.
-Low or absent NK cell activity.
-Ferritin > 500 ng/mL
- CD25 > 2400 U/mL

times can be prolonged sometimes leading to disseminated intravascular coagulation (DIC). Our patient presented several of these alterations; however, once the treatment was started, all parameters normalized rapidly [37, 41].

In order to make an early diagnosis, it is essential to assess any organ involvement with a full physical examination and ancillary laboratory and diagnostic imaging tests. Overlapping infections or conditions should be ruled out. Once the patient is stable, a complete familial history should be performed. Initial evaluations should include a blood count, coagulation panel, serum ferritin levels, urinalysis, liver and kidney function, urine and blood cultures, a chest radiograph and an electrocardiogram. In order to evaluate multiple organ damage, it might also be necessary to perform an echocardiogram, a bone marrow aspirate, a lumbar puncture, a brain magnetic resonance imaging and a body CT scan [37].

Bone marrow aspiration and a biopsy are useful to investigate the cause for cytopenia, as well as to rule out infections or malignancy. The findings of hemophagocytosis and activated macrophages with a benign appearance are consistent with HLH but not pathognomonic. However, in cases of high suspicion and a negative result, a liver, spleen, skin or lymph node biopsies are justified. The lack of macrophagic invasion does not rule out HLH; the following conditions can be responsible for a false negative: an early biopsy before the disease has produced an infiltrative process; the administration of immunosuppressive therapies; and a recent blood transfusion [42, 43].

The immunologic assessment includes levels of soluble IL-2 receptor-α (they correlate with the degree of disease activity), NK cell function/degranulation and flow cytometry for cell surface expression of serum amyloid P component (SAP) and X-linked inhibitor of apoptosis protein (XIAP) in males. Genetic and HLA testing should be performed if available. Our patient was negative for mutations in perforin 1 (pore-forming protein) (PRF1), protein unc-13 homolog D (UNC13D), syntaxin 11 (STX11) and syntaxin

binding protein 2 (STXBP2) genes and NK cytotoxic activity. The existence of other mutations that are potential causes of HLH is likely; however, most of them have not yet been identified [44–46].

The current diagnostic criteria are based on the HLH trial published in 2004 [47] (Fig. 2). Many patients do not fulfill the criteria but actually suffer severe symptoms; therefore, it is necessary to start them on immunosuppressants as soon as possible. Early treatment is crucial and should not be delayed under any circumstance [1, 43].

It is important to evaluate the patient as a whole, taking into account the clinical context. The main goal is to suppress the severe inflammatory response that might be threatening the patient's life. Supportive treatment is always required, and it usually consists of prophylactic antibiotics, diligent fluid, electrolyte management and platelet transfusions. The basis of the immunosuppressive treatment includes dexamethasone, etoposide and cyclosporine A.

In addition to this, if there is evidence of neurological involvement, intrathecal methotrexate and prednisone are indicated. As renal failure is quite common, chemotherapy might require a dose adjustment. Cyclosporine is often withheld until the patient's renal function improves. After 8 weeks of treatment, either a bone marrow transplantation or a hematopoietic stem cell transplant is required in primary HS [1, 2, 37, 40].

In case of secondary syndrome, the management must be oriented to treat the underlying cause. When an autoimmune disease is present, immunosuppressive therapy must be initiated immediately; however, if there is an infectious agent involved (like our patient with CMV), immunosuppressive treatment should be withheld until the infection is under control, unless the patient is critically ill and other options have to be considered [32]. Etoposide is especially effective in HBV as it eliminates infected T lymphocytes [48]. In patients with less severe symptoms, adjuvant antibiotics, steroids and intravenous immunoglobulins might be enough [49] (Fig. 3).

Fig. 3 Representation of the main aspects for the treatment of HLH syndrome. *BM* bone marrow, *Ig i/v* intravenous immunoglobulin
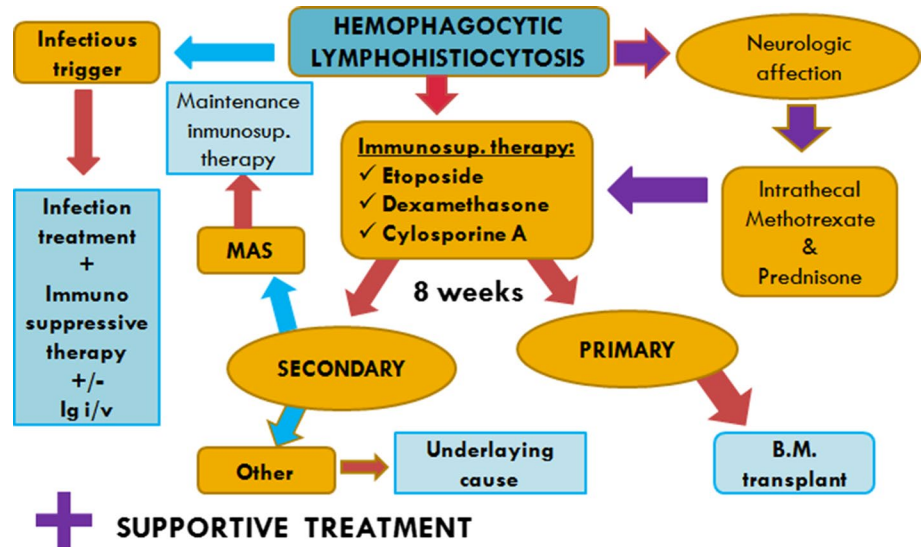
Marsh et al. [50] published a review of cases of patients treated with alemtuzumab that had not responded to standard treatment. An improvement in the survival rate was observed; however, the overall prognosis seemed to be worse.

Conclusion

HLH is a very rare syndrome but an important life-threatening condition. Laboratory findings and symptoms are not very specific, so it is essential to learn how to suspect it in order to make an early diagnosis and stop its fatal course. It could be deduced that this patient may have been predisposed to developing HLH from the underlying undiagnosed connective tissue disease which was "unmasked" by the acute viral infection.

Compliance with ethical standards

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