

HLH caused by an HSV-2 infection: a case report and review of the literature

E.M. Jongbloed^{1*}, M.A.W. Hermans², M. Wabbijn¹, J.J.A. van Kampen³, J.A.M. van Laar²

¹Department of Internal Medicine, Ikazia Hospital, Rotterdam, the Netherlands; Departments of ²Internal Medicine and Immunology, Section of Clinical Immunology, ³Viroscience, Erasmus Medical Center, the Netherlands. *Corresponding author: lisajongbloed@gmail.com

ABSTRACT

Haemophagocytic lymphohistiocytosis (HLH) is a rare hyperinflammatory condition that can be triggered by infections, malignancies, or auto-immune diseases. Here, we present a patient with rapidly progressive HLH triggered by a herpes simplex virus type 2 (HSV-2) primary infection. The patient was successfully treated with intravenous high-dose acyclovir, immunoglobulins, and dexamethasone. This is the first report of HSV-2-associated HLH in an immunocompetent adult patient.

KEYWORDS

Haemophagocytic lymphohistiocytosis, HSV-2

BACKGROUND

Haemophagocytic lymphohistiocytosis (HLH) is a rare, but potentially fatal hyperinflammatory condition that is often not recognised due to a lack of awareness among physicians. It can present with nonspecific symptoms including fever, cytopenias, and multiple organ failure. The diagnostic guidelines by the Histiocyte Society in 1991¹ are recognised, but their sensitivity and specificity were never validated.

HLH can be triggered by inborn disorders of the cytotoxic leucocytes, haematologic malignancies, auto-immune disorders, medication, or infections. Herpes viruses are associated with HLH:² Epstein-Barr virus, cytomegalovirus, and human herpesvirus-8 infections are the most often reported triggers, in both immunocompetent and immunodeficient patients. However, herpes simplex virus type 2 (HSV-2)-related HLH is rare. Here, we present a patient with rapid progressive HLH caused by an HSV-2 primary infection.

What was known on this topic?

Haemophagocytic lymphohistiocytosis (HLH) is a rare, but potentially fatal hyperinflammatory condition which can present with nonspecific symptoms including fever, cytopenias, and multiple organ failure. HLH can be triggered by inborn disorders of the cytotoxic leucocytes, haematologic malignancies, auto-immune disorders, medication, or infections.

What does this add?

HLH caused by a disseminated HSV-2 infection is rarely described in immunocompetent patients. If clinically suspected, HSV serology and PCR should be screened in patients with idiopathic HLH. HSV-2-associated HLH has a relatively good prognosis when adequate anti-viral and immunosuppressive therapy is started at an early stage.

CASE PRESENTATION

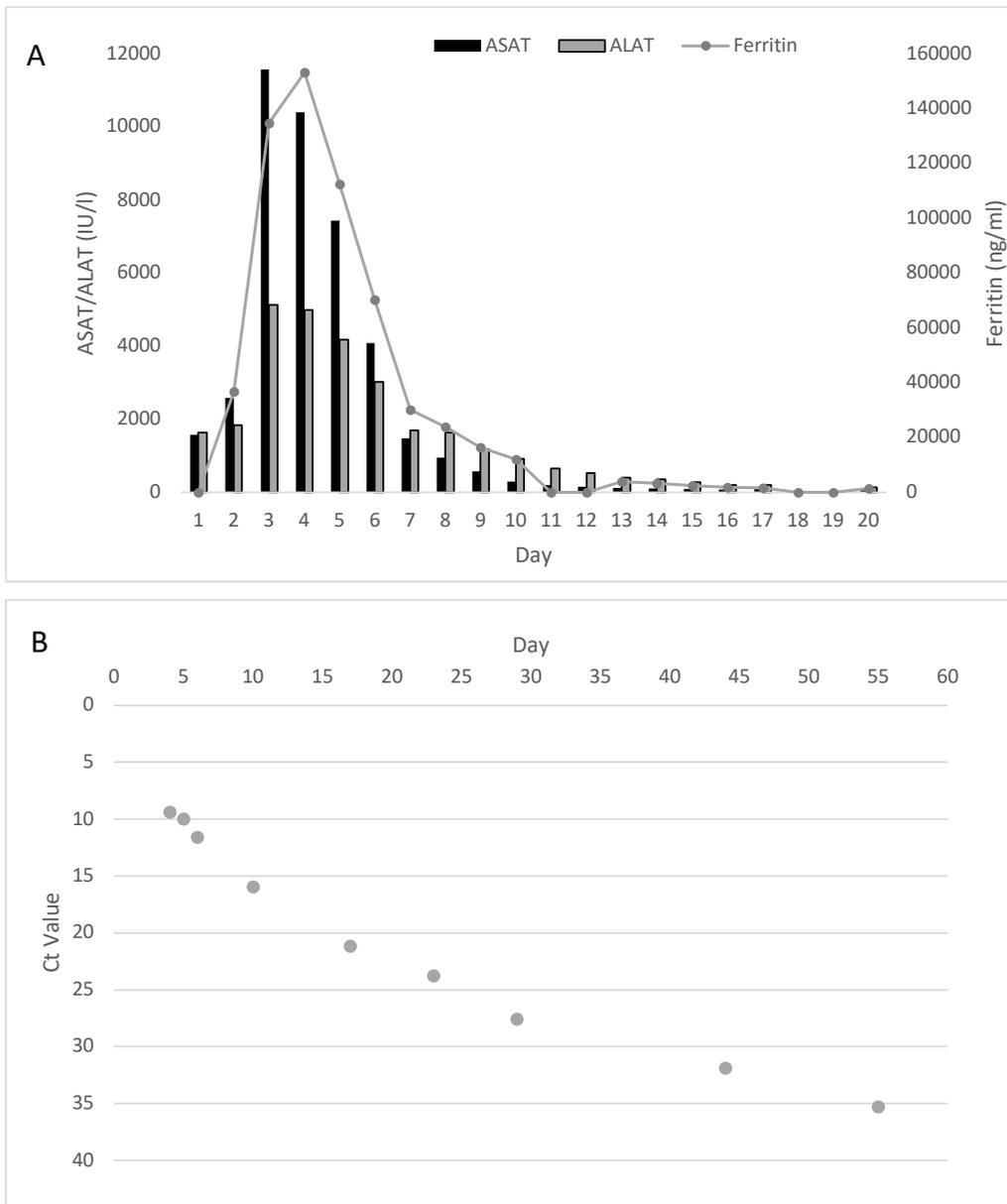
A 63-year-old woman presented with acute fever, confusion, and progressive right upper quadrant pain. Her medical history included hypothyroidism and chronic lower back pain. She had consulted her general practitioner two days prior because of fever and dysuria, and amoxicillin/clavulanate was started to treat a presumed urinary tract infection. An additional history revealed unsafe sexual intercourse with a new partner one week before the onset of her current symptoms.

On general examination, a severely ill patient with a fever of 39 °C and genital ulcers were seen. Palpation of the right upper quadrant of the abdomen was painful without signs of peritonitis. She had no lymphadenopathy or organomegaly.

Initial blood investigations showed a mild thrombopenia (thrombocytes of $123 \times 10^9/l$), leucopenia (white blood cell count of $3.7 \times 10^9/l$), and a non-icteric hepatitis (alanine aminotransferase (ALT) of 1628 IU/l and aspartate aminotransferase (AST) of 1566 IU/l). Cefuroxime was started to treat a sepsis of unknown origin.

A CT scan of the abdomen showed a normal aspect of the gallbladder but a wide common bile duct and multiple liver cysts, and some prominent lymph nodules around the mesenteric vessels. An endoscopic ultrasound was performed, which showed acalculous cholecystitis but no signs of biliary obstruction.

Figure 1. Clinical course. Treatment with acyclovir, IV immunoglobulins, and dexamethasone was started on day 3. Changes of ASAT, ALAT, and ferritin (A). Course of HSV-2 load in plasma (B). Cycle threshold (Ct) values are inversely correlated to the HSV-2 load. A Ct value of > 45 means that the PCR result is negative.



ALAT = alanine transaminase; ASAT = aspartate aminotransferase; HSV-2 = herpes simplex virus type 2; IV = intravenous

During the second day of admission, the liver enzymes and bilirubin level increased rapidly (ALT of 1830 IU/l and AST of 2581 IU/l). The presence of hyperferritinaemia (36,700 ng/ml) and progressive pancytopenia led to the suspicion of HLH that was confirmed by a bone marrow aspirate. Simultaneously, liver failure progressed and the patient was transferred to the nearest academic medical centre. There, a primary infection with HSV-2 was shown: IgM antibodies against herpes simplex virus without IgG antibodies. Additionally, a PCR assay of the EDTA plasma was strongly positive for HSV-2 but negative for herpes simplex virus type 1. A subsequent liver biopsy also showed HSV-2 infection, confirmed by immunohistochemistry, with chronic infiltration and necrosis of 40% of the liver parenchyma with focal haemophagocytosis. Treatment with intravenous high-dose acyclovir (10 mg/kg, 3 times daily), intravenous immunoglobulins and dexamethasone was started on hospital day three. The fever quickly subsided and the liver enzymes started to improve after two days (figure 1, panel A). The HSV-2 load decreased during and after hospital admission, whereby the HSV-2 DNA was still detectable after three months (figure 1, panel B).

The patient showed a rapid recovery and was discharged 32 days after initial presentation. Oral valacyclovir was continued until one month after discharge. The dexamethasone was gradually tapered and was finally discontinued after 74 days of treatment.

DISCUSSION

Here, we describe a patient with HLH and acute fulminant liver failure after a primary genital HSV-2 infection. HSV-2 is a common sexually transmitted disease that is usually self-limiting and asymptomatic, but can result in a more serious infection depending on the immune status of the host.³ Acute hepatitis with liver failure is a rare complication that can be seen in patients with an HSV infection, either both HSV-1 or HSV-2.⁴ In our case, the patient developed fulminant liver failure within three days caused by both HSV-2 and reactive haemophagocytosis. The liver enzymes improved, accompanied by a decreasing HSV-2 viral load rapidly after anti-inflammatory and anti-viral treatment.

Table 1. HLH and HSV-2: five reported cases

Year	Author	Sex	Age	Underlying condition	Concomitant immunosuppressive medications	Primary infection or reactivation?	Treatment	Course of disease
2005	Yamaguchi	Female	Unknown	Pregnant	None	Unknown	Acyclovir, prednisolone, IVIG, and cyclosporine	Patient improved after administration of cyclosporin in a few days
2006	Ramasamy	Female	33	Bone marrow failure syndrome	Oxymetholone and prednisolone	Unknown	Acyclovir, immunoglobulins, broad spectrum antibiotics	Patient developed multi-organ failure and died a few days after starting with acyclovir and immunoglobulins
2016	Ikumi	Male	56	Multiple sclerosis	Fingolimod and methylprednisolone pulse therapy	Primo	Unknown, no antiviral therapy because no diagnosis of HSV-2	Patient died 18 days after admission, diagnosis settled with autopsy
2018	Nasser	Female	36	Pregnant	None	Primo	Acyclovir, dexamethasone	Clinical improvement in a few days
2019	Kurosawa	Male	46	Hypereosinophilic syndrome	Prednisolone and azathioprine	Unknown	Acyclovir, methylprednisolone	Clinical improvement in two weeks, discharge on day 22 after admission

HSV-2 = herpes simplex virus 2; IVIG = intravenous immunoglobulin

We searched the literature for cases of HSV-2-associated HLH. We used the Pubmed search engine and selected all cases that fulfilled the current HLH criteria and were written in English. There are five previously reported cases of HLH caused by a disseminated HSV-2 infection, of whom two patients had a certain primary infection (table 1).⁵⁻⁹ Three of the five described patients were using immunosuppressive therapies because of their underlying disease. Two cases report a pregnant woman without a relevant medical history. Pregnancy might lead to a reduced immunity to herpes viruses due to the shift of a T-helper 1 to T-helper 2-dominated cell-mediated immunity and is often associated with an exaggerated inflammatory response to viral infections.^{8,9} In three cases, the patients were treated with acyclovir intravenously, and cessation of immunosuppressive therapy and corticosteroids early in the course of the disease, and all three patients recovered with no reported signs of recurrence of HLH.^{6,8,9} In one case, the diagnosis was established relatively late, and therefore the start of adequate treatment was delayed, leading to the death of the patient.⁷ In the fifth case, the diagnosis of HSV-2-associated HLH was made on autopsy.⁵ Remarkably, our patient did not use immunosuppressive agents. Her medical history and further analysis did not reveal any signs of immunodeficiency; the patient had normal immunoglobulin levels, normal levels of CD4+ and CD8+ T cells, and no human immunodeficiency virus infection. Furthermore, whole-exome sequencing did not reveal any known mutations that are associated with HLH or immunodeficiency in general. Five months after these episodes, there is still no sign of immune deficiency. Therefore, it is presumed that reactive HLH has complicated a primary HSV-2 infection in a previously immunocompetent patient. Treatment of adult patients with HLH is challenging because no general guidelines exist. It is recommended

to treat the underlying cause together with immunosuppressive treatment in a multidisciplinary referral centre with expertise in adult HLH patients. Cautious monitoring and swift adjustment in cases of progressive signs of the HLH is warranted to achieve complete regression of the potentially fatal hyperinflammatory state.¹⁰ In cases of HLH caused by a disseminated HSV-2 infection, which is rarely described in an immunocompetent person, differentiating between HLH and primary severe HSV-induced hepatitis remains challenging. Both cytopenia and hyperferritinaemia could be caused by hepatitis due to hepatocellular damage. The differentiation is important because of treatment implications.¹¹ Evidence of haemophagocytosis in the bone marrow and hypertriglyceridaemia may point towards HLH, although this hypothesis cannot be corroborated with clinical evidence since this has never been studied.

In conclusion, this is the first report of HSV-2-associated HLH in an immunocompetent adult patient. If clinically suspected, HSV serology and PCR should be screened in patients with idiopathic HLH. Although HLH is a severe condition with a high rate of morbidity and mortality, the prognosis of a patient with HSV-2 largely relies on the early recognition and treatment of the HSV infection. Based on previously reported cases and the case reported here, HSV-2-associated HLH could have a relatively good prognosis when adequate anti-viral and immunosuppressive therapy is started at an early stage.

DISCLOSURES

All authors declare no conflicts of interest. No funding or financial support was received. Informed consent: written informed consent of the patients was obtained.

REFERENCES

- Henter J-I. The FHL Study Group of the Histiocyte Society. Diagnostic guidelines for hemophagocytic lymphohistiocytosis. *Semin Oncol.* 1991;18:29.
- Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet.* 2014;383(9927):1503-16.
- Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med.* 1983;98(6):958-72.
- Pinna AD, Rakela J, Demetris AJ, Fung JJ. Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci.* 2002;47(4):750-4.
- Ikumi K, Ando T, Katano H, et al. HSV-2-related hemophagocytic lymphohistiocytosis in a fingolimod-treated patient with MS. *Neurol Neuroinflammation.* 2016;3(4):e247.
- Kurosawa S, Sekiya N, Fukushima K, et al. Unusual manifestation of disseminated herpes simplex virus type 2 infection associated with pharyngotonsillitis, esophagitis, and hemophagocytic lymphohistiocytosis without genital involvement. *BMC Infect Dis.* 2019;19(1):65.
- Ramasamy K, Lim ZY, Savvas M, et al. Disseminated herpes virus (HSV-2) infection with rhabdomyolysis and hemophagocytic lymphohistiocytosis in a patient with bone marrow failure syndrome. *Ann Hematol.* Springer; 2006;85(9):629-30.
- Yamaguchi K, Yamamoto A, Hisano M, Natori M, Murashima A. Herpes Simplex Virus 2-Associated Hemophagocytic Lymphohistiocytosis in a Pregnant Patient. *Obstet Gynecol.* 2005;105(5):1241-4.
- Nasser MF, Sharma S, Albers E, Sharma S, Duggal A. Pregnancy-related Hemophagocytic Lymphohistiocytosis Associated with Herpes Simplex Virus-2 Infection: A Diagnostic Dilemma. *Cureus.* 2018;10(3).
- La Rosée P, Horne A, Hines M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood.* 2019;133(23):2465-77.
- Liew JW, Jones BL, Hunter AJ. Disseminated Herpes Simplex Masquerading as Hemophagocytic Lymphohistiocytosis: A Case Report. *Perm J.* 2019;23.