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CASE REPORT

Severe hepatitis with coagulopathy due to HSV-1 in an immunocompetent man

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ABSTRACT

Severe hepatitis due to herpes simplex virus type 1 (HSV-1) in immunocompetent patients is a very rare event. The acute hepatitis may lead to fulminant deterioration of liver function and can be rapidly fatal. The diagnosis should be considered in case of severe hepatitis of unknown cause. Early consideration of HSV-1 hepatitis in the differential diagnosis in an adult patient, also with an apparently normal immune system, is important and early initiation of antiviral treatment may be lifesaving in this situation.

KEYWORDS

Herpes simplex infection, hepatitis, HSV-1, immunocompetent

What was known on this topic?

Systemic herpes simplex infection with acute severe hepatitis is a rare complication of HSV-1 infection, especially in immunocompetent patients. The diagnosis is often missed due to the absence of specific signs or symptoms. Severe HSV-1 hepatitis is usually marked by significant elevations in transaminases (ASAT higher than ALAT), and a mild or absent hyperbilirubinaemia and coagulopathy. The course of the disease is often rapid and frequently fatal. The mortality rates are high mainly because of delayed diagnoses and treatment with antiviral therapy.

What does this case add?

This report is interesting, since it involves an immunocompetent patient with severe HSV-1 hepatitis. This patient recovered completely with adequate antiviral treatment with acyclovir. In a sudden onset of severe hepatitis of unknown aetiology, rapid initiation of antiviral therapy should also be considered in immunocompetent patients, especially when acute liver failure is suspected.

INTRODUCTION

Herpes simplex infection (HSV-1 or HSV-2) is a common and usually benign, self-limiting disease, which normally presents with mucocutaneous lesions and mild viraemia, although the primary episode can cause rather severe local infection.[1,2] Systemic herpes simplex infection with acute hepatitis is a rare complication of HSV-1 infection, especially in immunocompetent patients.[2] HSV hepatitis is often missed due to the absence of specific signs or symptoms. Clinical manifestations are nonspecific, which include flu-like illness, fever and abdominal discomfort. Severe HSV-1 hepatitis is usually marked by significant elevations in transaminases (aspartate aminotransferase (ASAT) higher than alanine aminotransferase (ALAT)), a mild or absent hyperbilirubinaemia, coagulopathy, encephalopathy and skin rash. The course of the disease is often rapid and frequently fatal. The mortality rate can be as high as 90%, mainly because of delayed diagnosing and treatment with antiviral therapy.[2,3]
We describe a rare case of a very sudden onset of severe hepatitis in an immunocompetent male with coagulopathy due to herpes simplex infection (HSV-1). This case illustrates that awareness of HSV-1 hepatitis, though extremely rare in immunocompetent patients, is important, since timely recognition and early initiation of antiviral therapy improves survival considerably.

CASE REPORT

A 57-year-old man, who had been ill for three days with fever, sweating and chills, was referred to our hospital. Ten days after his return from a nine-day vacation to Gambia

he became ill. He had taken malaria prophylaxis and he was vaccinated for DTP, hepatitis A and B. He had stopped smoking eight months ago and he had an alcohol intake of one drink per day.

Physical examination showed a blood pressure of 99/62 mmHg, a pulse of 76 beats/min, an oxygen saturation of 96% and a temperature of 38.5 °C. He was noted to have a few small vesicles in his neck. Lung and heart sounds were normal. During abdominal examination, no abnormalities were found. Laboratory assessment revealed a high C-reactive protein of 75 mg/l (<5), a low platelet count (102 x 10^9/l) and a leucocyte count of 5.4 x 10^9/l. Kidney function was normal. The liver functions where not measured on day 1 of hospitalisation. Chest radiography showed no abnormalities. Because of progressive fever, intravenous amoxicillin/clavulanic acid was started. Intravenous acyclovir was also initiated because of a clinical suspicion of a disseminated varicella zoster virus infection, given the skin lesions in his neck.

On day 2, laboratory test results revealed elevated transaminases (ASAT 1348 U/l, ALAT 852 U/l) with normal bilirubin 12 mmol/l. Leukopenia (2.4 x 10^9/l) and a low platelet count (69 x 10^9/ l) were found. Ultrasound examination showed a normal aspect of the abdominal organs. Although hepatitis due to the malaria prophylaxis was a possibility, a serious bacterial or viral infection was thought to be far more probable.

Bacterial and fungal cultures, including cultures of blood, urine and sputum were unrevealing. Malaria testing by antigen testing and microscopy were repeatedly negative. Serological tests for hepatitis A, B and C viruses, cytomegalovirus (CMV), Ebstein-Barr virus (EBV), influenza and human immunodeficiency virus showed no evidence of a recent infection with any of these viruses.

The patient's condition worsened during hospitalisation. There were signs of disseminated intravascular coagulation (INR: 2.2, prothrombin time (PT) 21 sec, fibrinogen 1.6 g/l, D-dimer: 70649 mg/l) with spontaneous gastrointestinal and urinary tract haemorrhages and respiratory failure with pleural effusion. On day 3 he was admitted to the intensive care unit with melaena and haemodynamic instability. He had severe hepatitis with maximum levels of transaminases: ASAT 4530 U/l and ALAT 1978 U/l. Acute liver failure was suspected, but hyperbilirubinaemia was absent (*table 1*), which made acute liver failure less likely.

Liver biopsy was not performed because of a high risk of bleeding and the absence of hyperbilirubinaemia. CT scan, thoracentesis and gastroscopy did not reveal other pathology. A crista biopsy was performed which revealed no signs of myelodysplasia.

African viral haemorrhagic fevers (VHF) such as Dengue, Lassa, Marburg and Ebola where considered. Given the clinical picture, however, there was no immediate suspicion of VHF. The Dengue antigen test was negative.

Table 1. *Laboratory values in the patient*

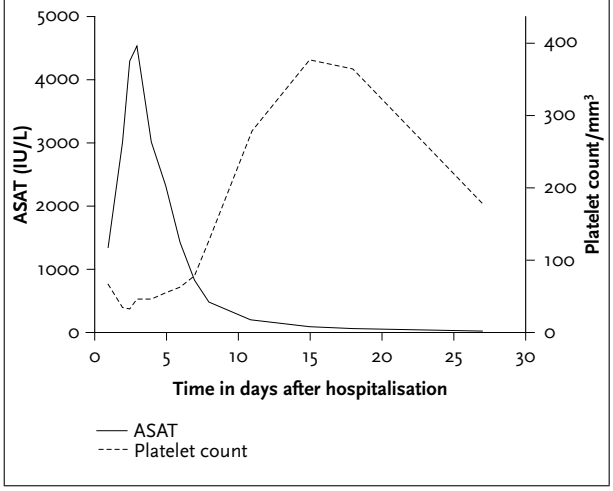
Time in days after hospital admission	1	2	3	18	Normal ranges
Haemoglobin	8.9	8.0	7.8	7.2	8.5-11.0
Leucocyte/mm³	5.4	2.4	2.0	4.0	4.0-10.0
Platelet/mm³	102	69	34	375	150-400
ALAT (IU/l)		852	2134	67	0-45
ASAT (IU/l)		1348	4292	40	0-40
LDH (IU/l)		1042	2134	331	0-250
Total bilirubin (µmol/l)		12	13	16	0-17
D-dimer (µg/l)			70649		0-500
Fibrinogen (g/l)		1.9	1.6		2.0-4.5
INR			2.2		0.8-1.2
APTT time/sec		21	59	31	26-34
Prothrombin time/sec		21		15	12-15
CRP (mg/l)	75	72	55	16	0-10

ALAT = alanine aminotransferase; APTT = activated partial thromboplastin time, ASAT = aspartate aminotransferase; CRP = C-reactive-protein; INR = international normalised ratio; LDH = lactate dehydrogenase.

The patient also developed a tremor and impaired consciousness, possibly caused by encephalitis.

On day 7 molecular analysis by polymerase chain reaction of EDTA blood revealed a high viral load (cycle value (CT): 17) of herpes simplex virus type I (HSV-1), which established the diagnosis of HSV hepatitis. Antibiotics were stopped and intravenous acyclovir (10 mg/kg of body weight every eight hours) was continued. On day 8 of intravenous acyclovir the patient started to improve clinically until full recovery, including normalisation of hepatic enzymes and coagulation (*table 1* and *figure 1*). HSV DNA was not measured over time, but a second EDTA-blood sample taken one day later than the first, analysed by a different laboratory, also revealed a high viral load (CT: 18.6) of HSV.

Figure 1. *Changes in serum aspartate aminotransferase (ASAT) and platelet count during hospital stay. Acyclovir is started on day 1*



DISCUSSION

In this report we present a case of an immunocompetent man with a very sudden onset of severe HSV-1 hepatitis with signs of disseminated intravascular coagulation (DIC).

HSV-1 is an uncommon cause of hepatitis. It is known that HSV-1 can induce hepatitis during pregnancy and in immunocompromised hosts.[4] To our knowledge, only eight cases of severe hepatitis due to HSV in immunocompetent adults have been reported.[2,5-7] HSV-1 hepatitis presents with nonspecific symptoms such as fever, headache, nausea, vomiting and abdominal pain. Diagnosis is often delayed because of absence of specific skin lesions. Previous reports have noted that mucocutaneous lesions are only present in up to 50% of cases.[2,8]

Strongly elevated liver enzymes, leukopenia, relatively low bilirubin level with DIC and mucosal herpetic lesions are clues to the diagnosis. The triad of fever, elevation of transaminases and presence of leukopenia is suggestive of a viral hepatitis such as herpes simplex hepatitis. The pathogenesis of fulminant HSV-1 hepatitis is unknown. Proposed mechanisms include an impaired immune system or infection with a particular virulent strain.[8,13]

The diagnosis of HSV-1 hepatitis should be considered in any patient with acute hepatitis, particularly with fever, leukopenia, and a negative hepatitis serology for hepatitis A, B, C, D, E,[9] EBV and CMV especially when DIC is present and liver failure is suspected.[11,12] A definitive diagnosis was made ante-mortem in only about one-third of the patients with a severe HSV hepatitis reported in the literature.[13]

Liver biopsy is the gold standard to diagnose HSV hepatitis, but is often contradicted in the context of coagulopathy.[4] Transjugular liver biopsy minimises the risk of bleeding and should be considered if DIC is present to accelerate the diagnosis, which could be lifesaving. Beersma *et al.* illustrated that quantification of HSV DNA levels by PCR in plasma or EDTA blood is a fast, sensitive and specific test to diagnose HSV hepatitis in patients with acute liver failure.[13] Rapid initiation of antiviral treatment is associated with improved outcomes in patients with HSV hepatitis.[12,13] This case underscores the need for early consideration of HSV-1 hepatitis in the differential diagnosis in an adult patient with an apparently normal immune system. Early initiation of acyclovir, although given because of a suspicion of generalised varicella-zoster virus infection, might have been lifesaving in this case.

CONCLUSION

In conclusion, severe hepatitis due to HSV in immunocompetent patients is a very rare event and is rapidly fatal, if unrecognised and not treated with intravenous acyclovir. This case illustrates that, in case of severe hepatitis of unknown cause, rapid initiation of antiviral therapy should be also considered in immunocompetent patients, especially when acute liver failure is suspected.

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