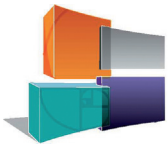
Anaesth Crit Care Pain Med 38 (2019) 77–78



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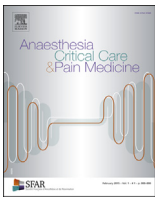

Letter to the Editor

Herpes simplex virus: A rare but treatable cause of fulminant hepatitis

Acute liver failure (ALF) is a life-threatening disease mostly triggered by drug-induced toxic liver damage or viral hepatitis. In a large cohort study including 1147 US patients, the main ALF causes were acetaminophen (46%), undetermined cause (14%), drugs (11%), hepatitis B virus (7%), autoimmune hepatitis (5%), hepatitis A virus (3%) and Wilson disease (2%) [1]. Herpes simplex virus (HSV) hepatitis accounts for only 1% of ALF episodes and only 2% of viral ALF. Most adult cases are associated with cell-defect immunity (renal transplant, pregnancy in the third trimester, AIDS, cancer, immunosuppressive agents). Although most HSV-related ALF developed in immunocompromised patients, Norvell et al. showed in a retrospective study of 137 HSV hepatitis that 23% were apparently immunocompetent [2]. HSV hepatitis is the most lethal complication of HSV infection in adults leading, in the absence of specific therapy, to mortality rates up to 75%. Despite an accessible specific treatment, this poor prognosis is partly explained by a frequently delayed diagnosis.

We report the case of a woman who developed a fatal HSV-associated ALF to help clinicians recognise more promptly this very severe disease and encourage them to treat patients in a timely manner.

A 68-years old woman with no relevant medical history presented to the emergency department for a Garden IV right hip fracture treated by total hip replacement surgery. The anesthesia protocol included intravenous propofol, sufentanil, atracurium, and inhaled sevoflurane. Neither hypotension nor hypoxia was reported. Forty-eight hours later, she developed fever at 38.4 °C. There was no clinical evidence of pulmonary, urinary tract or surgical site infections but a urinary sample culture recovered two strains of *Escherichia coli* and *Proteus mirabilis*. Intravenous ceftriaxone was then started for one day followed by oral cefixime. Five days after the initiation of antimicrobial therapy, her clinical condition worsened with a 40.5 °C body temperature associated with a shock that required crystalloid fluids resuscitation. Antibiotics were switched for piperaciline-tazobactam and she was admitted to the intensive care unit (ICU). Laboratory tests showed pancytopenia: leucopenia (1.7 G/L), lymphopenia (0.380 G/L), neutropenia (1.080 G/L), thrombocytopenia (148 G/L) and anaemia (haemoglobin 10.3 g/dL). Liver function tests showed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at 11,804 UI/L and 4414 UI/L, respectively, alkaline phosphatase (AKP) at 243 U/L and total bilirubin at 20 umol/L. ALF was confirmed by the decrease of prothrombin time (PT) from normal at admission to 48% then rapidly < 15% two days later. Intravenous N-acetyl cysteine was started.

Serological tests for hepatitis viruses A, B, C, HIV, and HSV were negative. In addition, serum hepatitis B, C, E virus, cytomegalovirus, and Epstein Barr virus polymerase chain reaction [PCR] were all negative. Auto-antibodies including antinuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-mitochondrial antibody [AMA] and anti-A liver/kidney microsomal antibody [LKM] were not detectable. Serum coeruloplasmin and copper concentrations were normal. No acetaminophen was found in plasma. Blood cultures were negative, chest X-ray was normal. A hepatic ultrasound showed no evidence of acute or chronic hepatic disease, and Doppler examination showed normal flow in hepatic veins. Few hours later, fulminant hepatitis was attested by the presence of grade three hepatic encephalopathy, leading to a multiple organ failure complicated by gastro-intestinal bleeding and hemorrhagic refractory shock. She died at day 10 after surgery, 3 days after the onset of ALF. Post-mortem liver biopsies showed a diffuse hepatocytes necrosis (90%) associated with an intense immunostaining for herpes simplex virus 1/2 (HSV1/2). The HSV1 serum PCR was retrospectively positive with a very strong signal.

This case highlights the challenging issue of HSV hepatitis diagnosis. Whereas HSV ALF occurs mostly in immunodeficient patients, this was not the case of our patient. However, since no autopsy was performed, the hypothesis of a subclinical cancer or haematologic disorder cannot fully be discarded. In addition, as drug-induced ALF is frequently encountered, we carefully reviewed all antibiotics (ceftriaxone, cefixime), analgesic drugs (nefopam, tramadol and morphine but no acetaminophen) without obvious causal relationship. At the time of surgery, mild lymphopenia could be retrospectively considered as a warning sign. The first clinical manifestation (fever) appeared only a few days later.

In the literature, this very rare diagnosis is frequently made through post-mortem biopsy (58%) [2], because of the lack of specific symptoms, particularly HSV skin eruption which is present only in 44% of cases [2]. Furthermore, serological test can be negative despite true HSV infection. Liver biopsies are considered the gold standard for HSV hepatitis, but percutaneous biopsies are often contra-indicated in the context of coagulopathy. Transjugular liver biopsies should be discussed in an adequate environment including a trained operator and a team involved in liver-transplantation. In ALF, unlike the last guideline from the American Association for the Study of Liver Diseases published in 2012 [3], the European Association for the Study of the Liver now recommends to screen for HSV hepatitis with quantitative PCR to hasten aciclovir (ACV) initiation [4]. qPCR could also be very useful during follow up to evaluate the effectiveness of antiviral therapy. Consecutive quantification of the HSV DNA load in plasma ACV-treated HSV hepatitis patients would promptly identify those with ACV refractory disease which must be switched to alternative anti-HSV drugs like foscarnet and cidovovir [4].

Since HSV hepatitis is one of the sole treatable ALF, early parenteral ACV initiation is critical. It will improve prognosis and lower risk of progression to death or liver transplant [2]. Because of the relative harmlessness of a short ACV course, some authors

https://doi.org/10.1016/j.accpm.2018.02.016

suggest starting empirical parenteral ACV in every unexplained ALF until an alternative diagnosis has been made or HSV excluded [2]. This makes sense especially in case of ALF associated with fever, skin rash, thrombocytopenia or lymphopenia (respectively present in 94% and 71% of HSV-ALF cases) [2].

In conclusion, HSV-related ALF is a very rare and potentially life-threatening disease. Clinicians should be aware of this diagnosis, which must be promptly confirmed by serum qPCR analysis. Aciclovir therapy should be started as soon as possible, probably before virology test results if the clinical and biological presentation is consistent with HSV induced ALF.

Disclosure of interest

The authors declare that they have no competing interest.

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Available online 1 March 2018