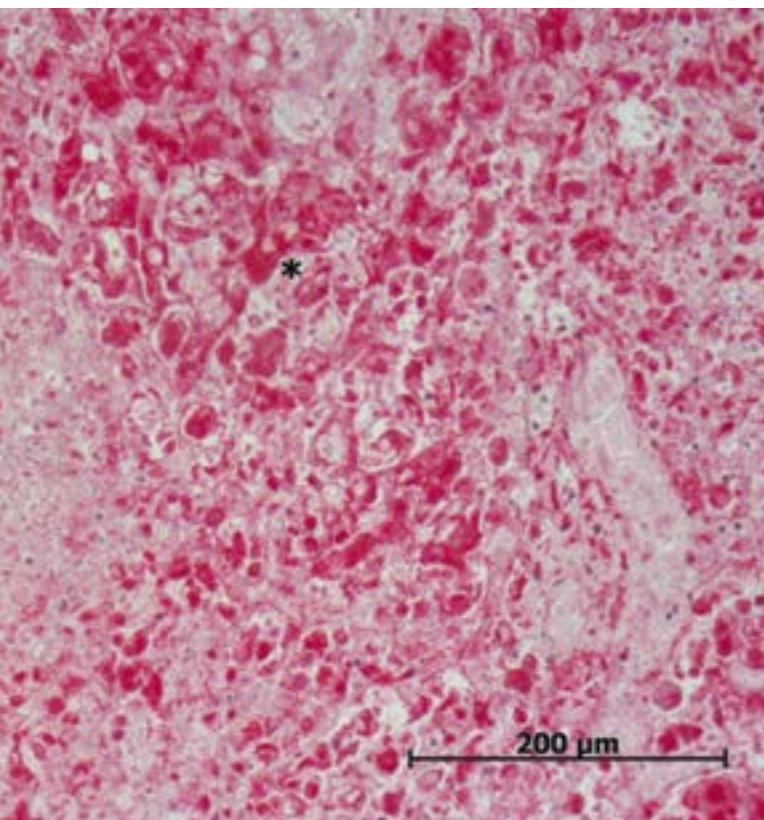


Fulminant hepatic failure in a neonate

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Although effective antiviral therapies are available for neonatal herpes simplex virus (HSV) disease, recent data demonstrate that no progress has been made in decreasing the interval between onset of HSV symptoms and initiation of antiviral therapy (1). We report a case of fatal neonatal HSV-2 infection presenting with fulminant hepatic failure despite a) an uneventful medical history concerning maternal HSV-2 infection and b) caesarean section before rupture of the membranes for suspected maternal appendicitis. Neonatal HSV-2 infection via maternal viremia must be included in the differential diagnosis of acute liver failure in newborns despite an unremarkable medical history concerning HSV-2 infection. To improve outcome, early antiviral treatment is warranted in these infants.

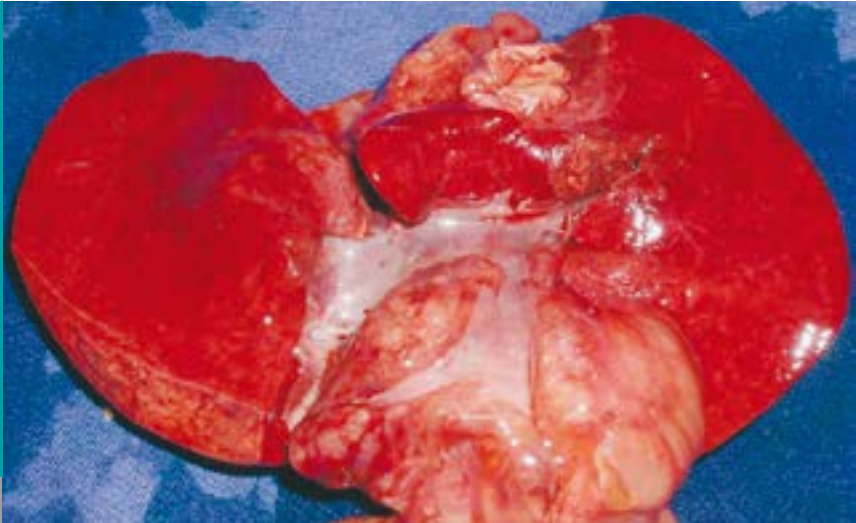


Fig. 2

Macroscopic appearance of the liver with scattered and partly confluent areas of severe liver necrosis.

CASE REPORT

A male Afro-American infant was delivered at 37 weeks of gestation by caesarean section, weighing 2,65 kg and subsequently breast-fed. Caesarean section was performed prior to membrane rupture for suspected maternal acute appendicitis. There was no history of maternal primary genital herpes infection. Post partum, the mother continued to be febrile for 3 days. Histopathological examination of the appendix, however, did not show signs of acute inflammation. The family history was unremarkable, except for portal vein thrombosis of unknown origin in the father. The mother and the infant were discharged home on day 3, but the neonate was readmitted to a local community hospital on day

10 because of hyperpyrexia (39.4° C), poor feeding and umbilical bleeding. Due to the development of generalized bleeding, the infant was then transferred to our hospital for suspected sepsis.

On admission, the infant was in shock and showed multiple hematomas. No oral or vesicular skin lesions were noted. There was a grossly enlarged liver with increased consistency. The patient required ventilatory and inotropic support. He was treated with broad-spectrum antibiotics. Initial investigations showed a white blood cell count of 3.7 G/l with neutropenia (neutrophils: 29%), thrombocytopenia 18 G/l and anemia (hemoglobin 95 g/l), and profound coagulopathy compatible with disseminated intravascular coagulation (thrombin time: 76 s; activated partial thromboplastin time: > 140 s, fibrinogen: < 0.2 g/l; d-dimers: 6450 ng/ml). Liver function test results showed the following serum concentrations: choline esterase 2.43 kU/l, total bilirubin 129 µmol/l, conjugated bilirubin 31 µmol/l, albumin 24 g/l, GPT 2232 U/l, glutamate dehydrogenase 3469 U/l, gamma-GT 261 U/l, lactate dehydrogenase: 13.340 U/l, and ammonia 3500 µg/l. The C-reactive protein was 17.5 mg/l, procalcitonin 2.2 µg/l. The patient had lactic acidosis (lactate 11.2 mmol/l). Serum ferritin was excessively elevated (124'840 µg/l) with a serum iron of 4.71 mg/l.

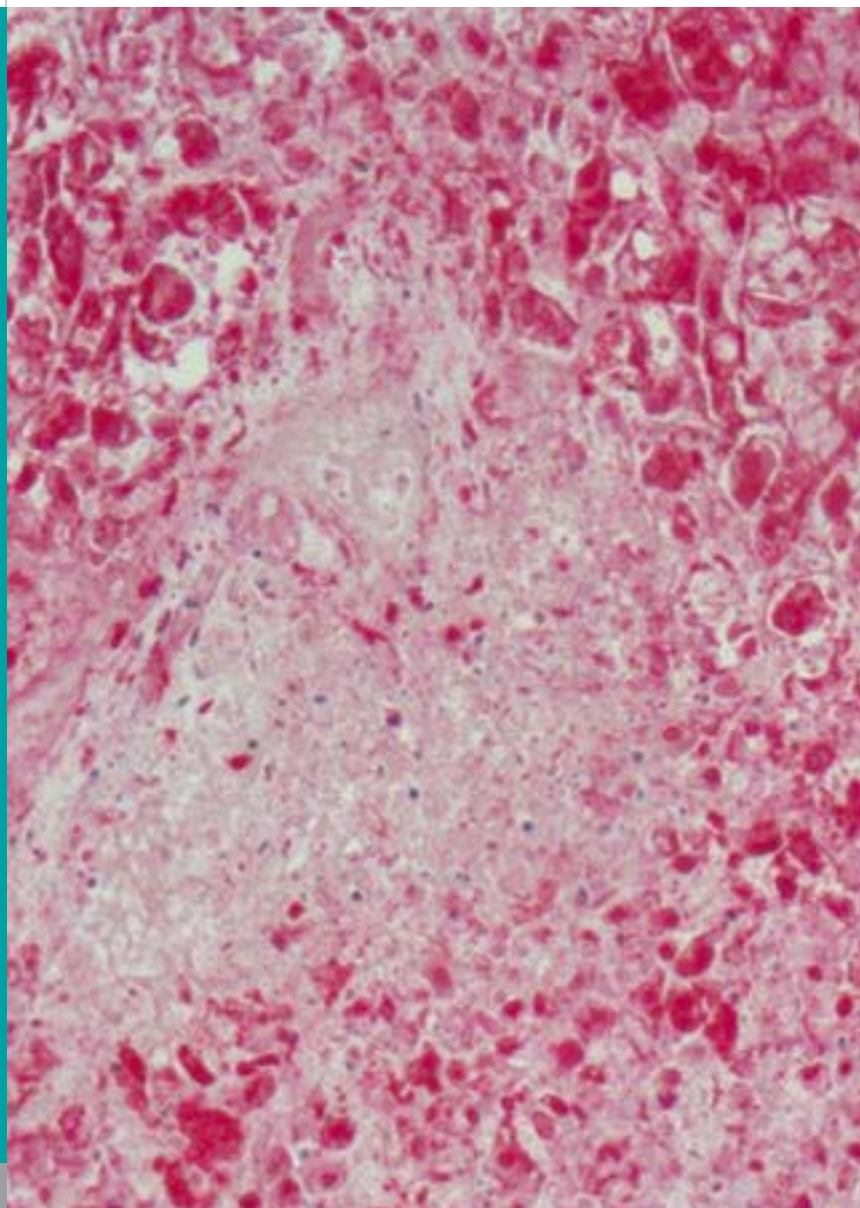
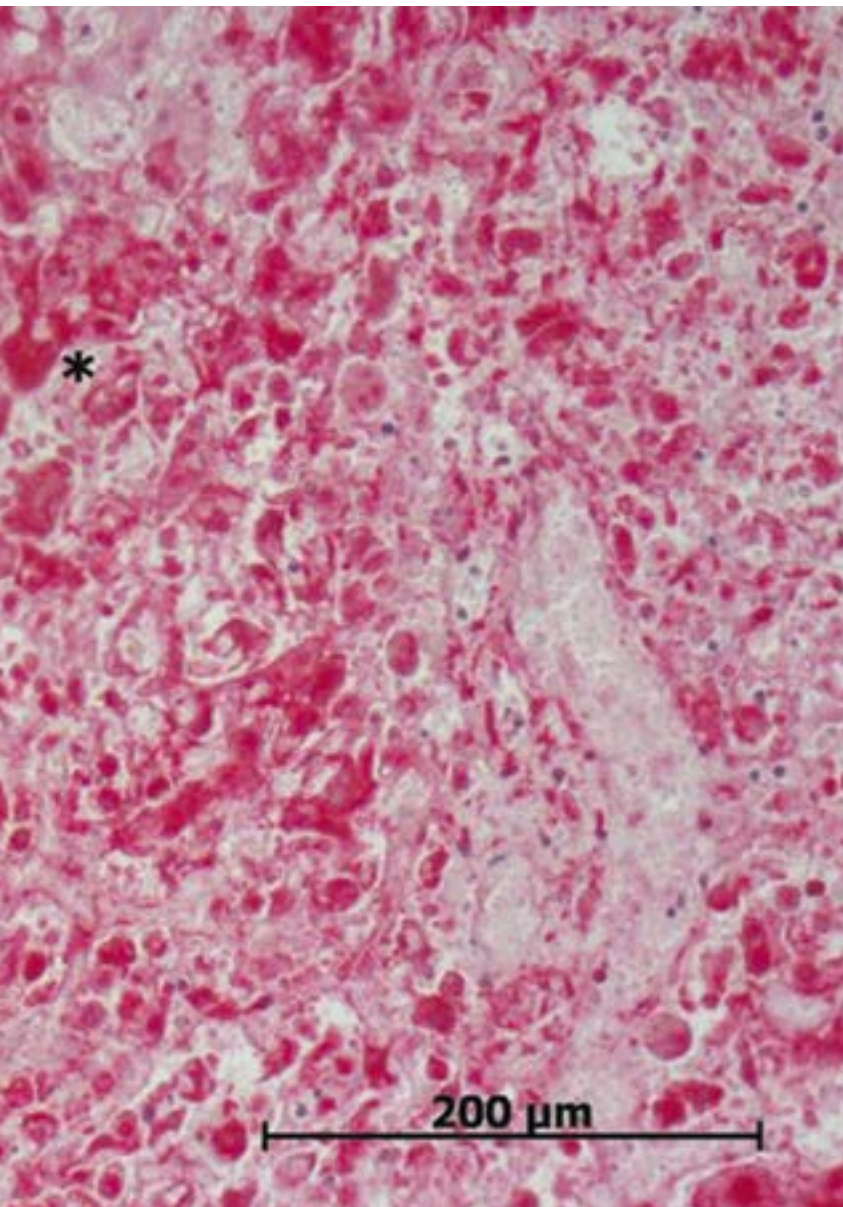


Fig. 2

Histopathology of the liver (HE-20) with immuno-histochemical proof of HSV-2 virus.



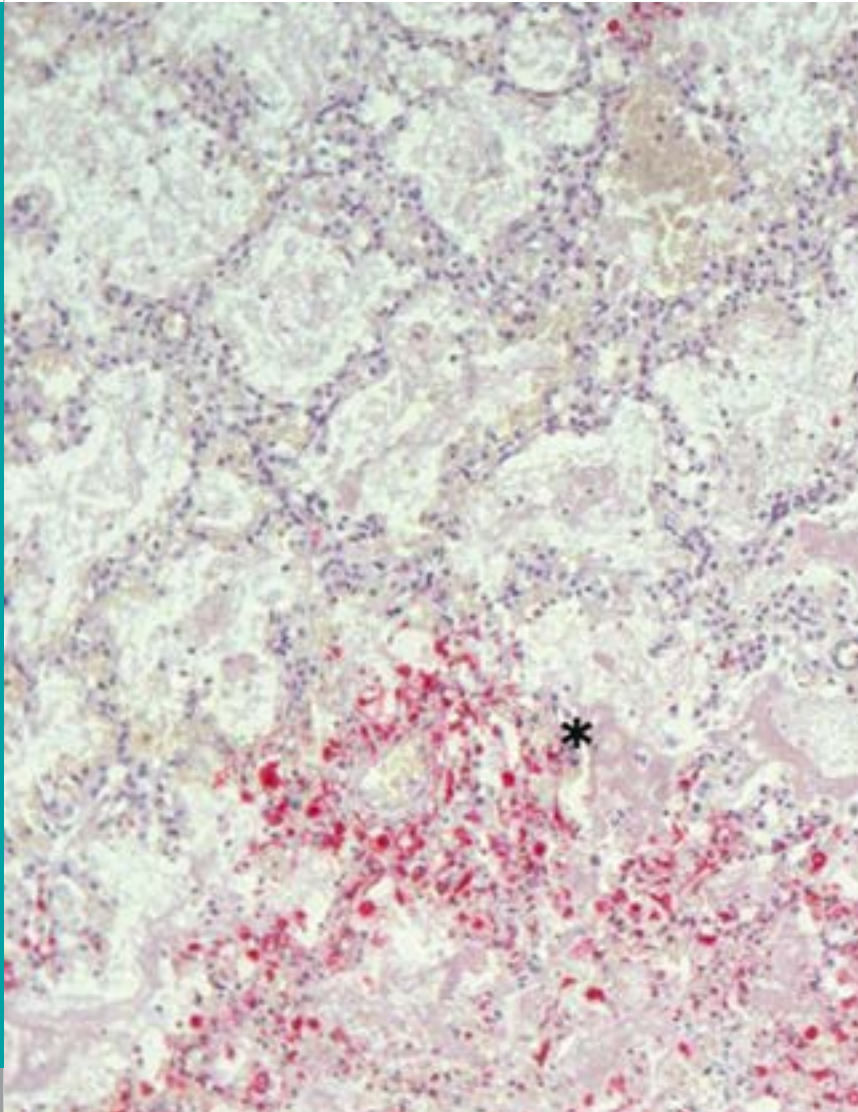
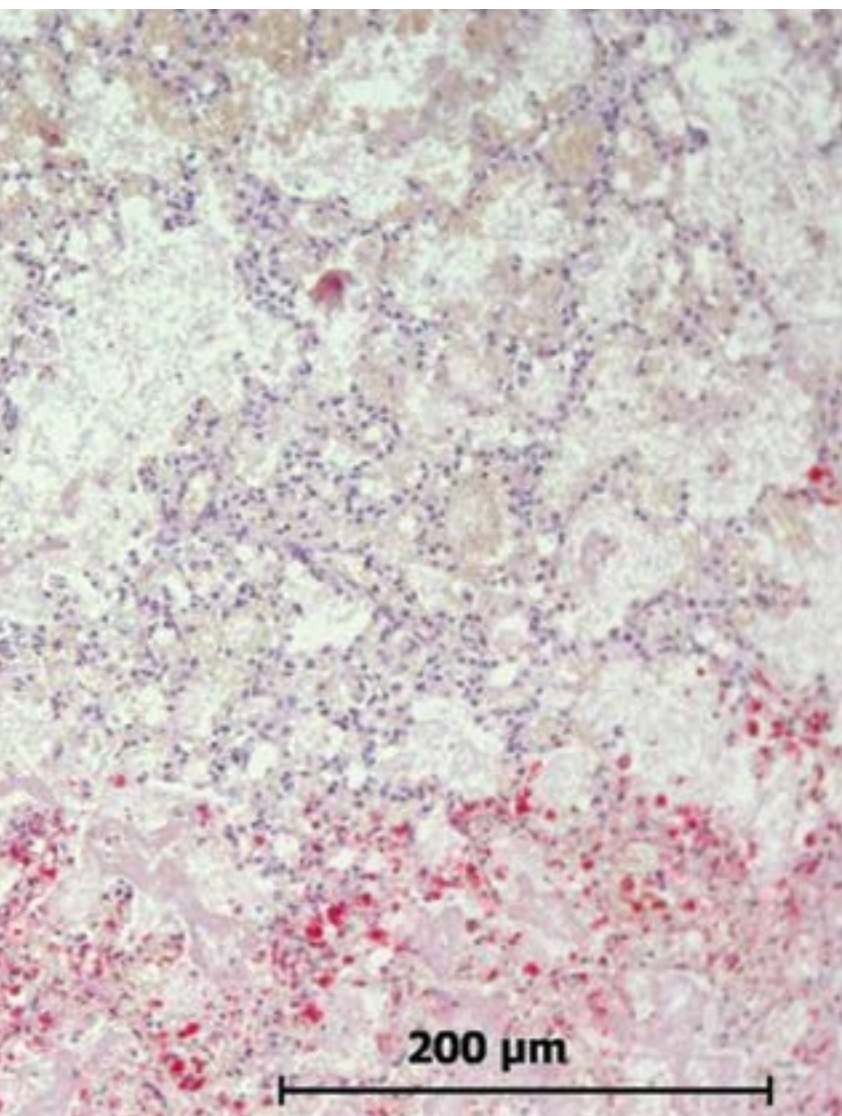


Fig. 3

Histopathology of the lung (HE-20) with immunohistochemical proof of HSV-2 virus (red stain, asterisk).



Herpes simplex virus 1 (PCR was available within 24 hours), hepatitis A, B, and C virus, Epstein-Barr-virus, human immunodeficiency virus 1 and 2, enterovirus, and cytomegalovirus infections were excluded using virologic or serologic methods. On ultrasonography, portal vein thrombosis was seen in this infant. Despite intensive supportive care consisting of substitution of platelets, fresh frozen plasma, PPSB, and the administration of sodium benzoate, carnitine, and N-acetylcysteine, the clinical course was aggravated by renal failure which required hemodialysis. The patient was proposed for liver transplantation, but died on day 5 after admission to our hospital in multiple organ failure. Pathological analysis of the liver demonstrated profound hepatic necrosis due HSV-2 infection (Fig. 1) which was proven by high counts of HSV DNA (1 billion HSV-2 copies/g liver and Fig. 2) - as well as HSV-2 pneumonitis (Fig. 3) and renal affection. Partial occlusion of the portal vein was confirmed by autopsy secondary to massive liver necrosis. The central nervous system was not infected by HSV-2.

Neonatal hemochromatosis and hemophagocytic lymphohistiocytosis were excluded by autopsy. Retrospective virologic examination for HSV-2 in the infant's urine and blood was positive. In the mother, a primary HSV-2 infection was diagnosed (HSV-2 IgG: negative, HSV-2 IgM: positive).

The known etiologies of fulminant hepatic failure in the neonate include hemophagocytic lymphohistiocytosis, metabolic, toxic, infectious, autoimmune, and ischemic causes, and neonatal hemochromatosis. Neonatal HSV-2 is usually acquired through intrapartum contact with infectious maternal genital secretions.

In the United States, HSV-2 infection rates are significantly higher in Blacks than in Whites (20.4 vs. 6.3 per 1'000) (2). The risk is highest in women who acquire a primary genital infection with either HSV type in the last trimester and have not yet developed type-specific antibodies at delivery (3). The risk of HSV-2 transmission can be decreased in these women by caesarean section to approximately 1,2% (4). Intravenous aciclovir given early in the course of the disease significantly improves prognosis. However, early diagnosis as in our patient may be difficult as the characteristic vesicular rash is absent in up to 40% of children, early symptoms are non-specific and the majority of the transmitting mothers lack a history of genital herpes. It must be taken into consideration, however, that maternal hematogenic transmission to the child via the umbilical vein probably resulted in infection of the liver as the primary target organ. An ascending infection, on the contrary, may more likely promote primary herpetic skin lesions. A definite diagnosis can only be established by virologic examination. In our patient HSV-1 was promptly ruled out, but HSV-2 infection erroneously was not taken into

the differential diagnosis due to the lack of maternal genital herpetic lesions, and caesarean section before rupture of the membranes.

Neonatal hemochromatosis is a disorder of intrauterine onset, manifests within the first hours or days after birth, and is associated with extrahepatic deposits of hemosiderin that spare the reticuloendothelial cells in the spleen, bone marrow, and lymph nodes. The serum ferritin concentration usually is markedly elevated in neonatal hemochromatosis as in our patient, but also is a non-specific finding in various forms of end-stage liver disease in both neonates and adults. Thus, the final diagnosis of neonatal hemochromatosis can only be made by tissue examination; however, due the clinical instability with generalized bleeding of our patient, we refrained from performing invasive procedures.

Due to hyperammonemia and elevation of serum lactate concentration, the initial putative diagnosis also included inborn errors of metabolism. However, galactosemia, fructose intolerance, tyrosinemia and urea cycle disorders could be excluded by appropriate means.

In summary, our case report emphasises the vital importance of HSV-2 infection as an etiology of acute liver failure in neonates. To improve outcome in infants with acute hepatic failure of initially unknown origin (viral, toxic, metabolic etc.) prompt initiation of antiviral therapy is warranted. Despite the fulminant

clinical course, early initiation of aciclovir administration might have had a favourable impact on the clinical course in our patient, thus gaining time for possible orthotopic liver transplantation.

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