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CASE REPORT

A Case Report of Acute Liver Failure in a Child with Hepatitis a Virus and Epstein-Barr Virus Coinfection on the Background of Autoimmune Sclerosing Cholangitis

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Background: Fulminant hepatitis is a rare and severe form of acute liver failure (ALF) characterized by rapid and massive destruction of liver cells and associated with a high mortality rate. Infectious factors, in particular viral hepatitis, take a prominent place in the etiology of ALF, however, the presence of chronic liver pathology can play a significant role in the disease progression and development of ALF.

Case Presentation: A 2-year-old child was hospitalized on the 4th day of the disease with manifestations of jaundice and general intoxication. The examination revealed markers of active hepatitis A virus infection and Epstein-Barr virus infection. From the seventh day of the disease, the child's condition began to progressively deteriorate due to manifestations of ALF. Despite the use of immunomodulatory and replacement therapy, the disease ended fatally on the 9th day. Pathohistological examination revealed manifestations of viral necrotic hepatitis on the background of autoimmune sclerosing cholangitis.

Conclusion: The case is novel as regards the occurrence of two viral hepatitis with different modes of transmission on a background of unidentified liver disease.

Keywords: acute liver failure, fulminant hepatitis, viral hepatitis A, Epstein-Barr virus infection, children

Introduction

Fulminant hepatitis is a rare and severe form of acute liver failure (ALF) characterized by rapid and massive destruction of liver cells and associated with a high mortality rate. According to the American Association for the Study of Liver Diseases (AASLD) guidelines, ALF is defined as a condition characterized by severe acute liver injury, coagulopathy, and hepatic encephalopathy that has developed within 26 weeks of disease onset in a patient without prior cirrhosis or evidence of chronic liver disease until appearance of symptoms.[1] Severe liver damage is indicated by an increase in serum transaminases and impaired liver function, which is manifested by jaundice and coagulopathy (international normalized ratio (INR) >1.5)).[2] Hepatic encephalopathy (HE) is characterized by changes in personality, consciousness, cognitive and motor functions. The severity of HE can range from subclinical disorders, detected only by neurophysiological and psychometric tests, to significant personality disorders, inappropriate behavior, and coma. The West Haven criteria are most often used to assess the severity of HE. According to this classification, four degrees of clinically expressed HE are distinguished. At the 1st degree, patients show attention deficit and some minor personality changes. At the II degree, disorientation in time, inadequate behavior and lethargy are noted. III degree is characterized by

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somnolence or stupor, disorientation to the place and situation, strange behavior. With IV degree, patients are in a coma. Patients with grade III and IV HE have an unfavorable prognosis.[3]

Among the causes of ALF, viral hepatitis and drug-induced hepatitis are the two most common worldwide. Other causes include hypoxia-induced liver injury, acute Budd-Chiari syndrome, veno-occlusive disease (in patients receiving chemotherapy), Wilson's disease, fungal poisoning, sepsis, autoimmune hepatitis, acute fatty liver of pregnancy, HELLP syndrome in pregnant women (hemolysis, elevated liver enzymes, low platelets), heat stroke and malignant infiltration of the liver (with metastases from breast cancer, small cell lung cancer and lymphoma).[4,5]

Among viral hepatitises, ALF is more often associated with viral hepatitis B (HBV) and hepatitis A (HAV). According to the WHO, there are about 1.5 million cases of HAV in the world every year.[6] Mostly, the disease proceeds as a self-limited infection with full recovery and the formation of stable immunity. In some cases, HAV can provoke ALF and have fatal consequences. WHO estimates about 7000 fatal cases of HAV. The adverse course is associated with older age (over 50 years) and chronic liver diseases.[7] The frequency of ALF among cases of HAV is up to 1%.[2] More than 800 cases of hepatitis A were registered in Ukraine in 2023.[8]

Epstein-Barr virus (EBV) infection usually has an asymptomatic or mild course in the form of infectious mononucleosis (IM) with fever, tonsillitis, lymphadenopathy, and hepatosplenomegaly. Liver damage in infectious mononucleosis is observed in 50–90% of patients and usually proceeds as a mild and self-limiting process, which is manifested by a moderate increase in the level of liver aminotransferases, hepatomegaly and jaundice. However, there are observations that EBV can occasionally be the cause of hepatitis with the development of ALF and a high risk of fatal outcome. The mechanism of liver damage in this infection is not entirely clear, but it is believed that liver damage in EBV infection is immunologically mediated by T-cell responses to EBV-infected B cells and infected CD8+ T cells.[9] About 1% of cases are associated with EBV in the structure of ALF in childhood.[10] EBV is widespread in Ukraine. More than 2000 cases of EBV have been reported in 2023.[8]

It is likely that HAV and EBV viruses can cause hepatitis with ALF in patients with an absolutely normal premorbid status. However, the fact that the same viruses cause ALF in some patients and not in others points to the important role of background genetic and environmental factors that increase the risk of an adverse course.

In this work, we describe a case of hepatitis in a child with ALF associated with coinfection of HAV and EBV against the background of autoimmune sclerosing cholangitis, who was hospitalized at the National specialized children's hospital of the Ministry of Health of Ukraine in 2023 in Kyiv, Ukraine.

Case Presentation

The parents of a previously healthy 2-year-old child came to our hospital with complaints of malaise, lethargy, vomiting, loose stools, yellowing of the sclera and skin, dark urine and white stools, which have been observed in the child for 4 days. Possible contact with infectious patients, use of drugs and other potentially toxic substances was not detected. The objective status of the child during hospitalization was characterized by elevated body temperature (37.7°C), marked lethargy, icteric coloration of the skin and mucous membranes, hepatomegaly. Heart rate (HR) – 123/min., respiratory rate – 24/min., SpO2-98%. The examination revealed an increase in total bilirubin to 129.6 μmol/l, direct fraction to 116.24 μmol/l, increased levels of transaminases: ALT - 4.5 mmol/l/h, AST - 3.3 mmol/l/h. Taking into account the clinical data, viral hepatitis was suspected, an appropriate examination and symptomatic therapy were prescribed.

Specific studies revealed positive titers of IgM HAV and IgM EBV (VCA), negative results of examination for markers of HBV (HBsAg), HCV (IgM+G), cytomegalovirus (IgM) and leptospirosis (PCR). An ultrasound examination revealed an increase in the size and increased echogenicity of the liver. Taking into account the detected markers, the disease was considered to be viral hepatitis A with EBV co-infection.

During the first three days of inpatient treatment, the child's condition remained stable, vital functions were within normal limits. In laboratory tests, there was a tendency to decrease the elevated levels of bilirubin and transaminases. On the fourth day of stay, a disturbance of consciousness appeared in the form of stupor (on the Glasgow coma scale (GCS) - (E3V4M5)=12b). The appearance of neurological symptoms was associated with deterioration of coagulation hemostasis indicators (Prothrombin index (PI), Activated partial thromboplastin time (APTT)), a decrease in the concentration of

protein in blood serum. The worsening of the condition was considered as ALF. The treatment included antibacterial therapy (cefotaxime 50 mg/kg/day), corticosteroids (dexamethasone 0.6 mg/kg/day), parenteral nutrition, replacement therapy (fresh-frozen plasma), albumin 20%, glutargin 80 mg/day, thioctic acid 10 units/kg/day, canavit up to 5 mg/day, respiratory support (ventilation). Over the next two days, the child's condition worsened due to ALF. Disturbances of consciousness progressed to severe coma (according to the FOUR (E0M0B0R1) scale = 1 point, without drug sedation), peripheral edema developed, hemorrhagic contents appeared through the nasogastric tube, intestinal peristalsis was suppressed, oligo-anuria developed, laboratory tests showed progression anemia, an increase in the level of indirect bilirubin, indicators of coagulation hemostasis worsened (Table 1). On the 6th day of hospital stay, the child had a cardiac arrest (asystole), which did not recover after resuscitation measures.

On the 4th day of inpatient treatment, a liver biopsy was performed. The pathohistological study revealed changes in the liver, which were characterized by the following changes: the beam structure is absent, the parenchyma with disturbed architecture due to widespread massive necrosis (Figure 1). When carrying out a histochemical reaction with Azan, soft-fibrous fibrosis in the parenchyma is noted (Figure 2). In immunohistochemical reactions with cytokeratin, the expression of biliary epithelium in the parenchyma in the form of false bile ducts is noted (Figure 3). Immunohistochemical reaction with CD45 and CD68 – diffuse expression of lymphocytic and macrophage cells in the parenchyma (Figures 4 and 5).

The results of histological examination were considered as manifestations of viral necrotic hepatitis against the background of autoimmune sclerosing cholangitis.

Table 1 Vital Functions and Results of Laboratory Tests

Indicator	Day from the Onset of Jaundice (Day of Inpatient Treatment)					
	4 (1)	5 (2)	6 (3)	7 (4)	8 (5)	9 (6)
Vital functions	Stable	Stable	Stable	Unstable	Unstable	Unstable
GCS (points)	15	15	15	12	4	1
Hemoglobin, g/l	117	110	102	101	97	71
Erythrocytes, g/l	4.23	4.22	3.70	3.88	3.73	2.66
Platelets, g/l	233	171	182	176	140	477
Leukocytes, g/l	6.1	12	6.8	5.0	7.9	10.8
Total bilirubin, μmol/l	538	340	270	305	328	310
Direct bilirubin, μmol/l	462	269	191	205	90	70
Indirect bilirubin, μmol/l	76	71	79	90	228	240
ALT, IU/l	998	1550	1290	1100	1120	900
AST, IU/l	900	1964	1830	1780	1024	950
Total protein, g/l	60	60	69	40	55	50
PI, %	90	85	50	60	40	30
APTT, sec	21	26	45	45	46	56
Fibrinogen, g/l	3	2	1.8	2.2	2.1	1.3

Abbreviations: *GCS, the Glasgow coma scale; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; PI, Prothrombin index; APTT, Activated partial thromboplastin time.

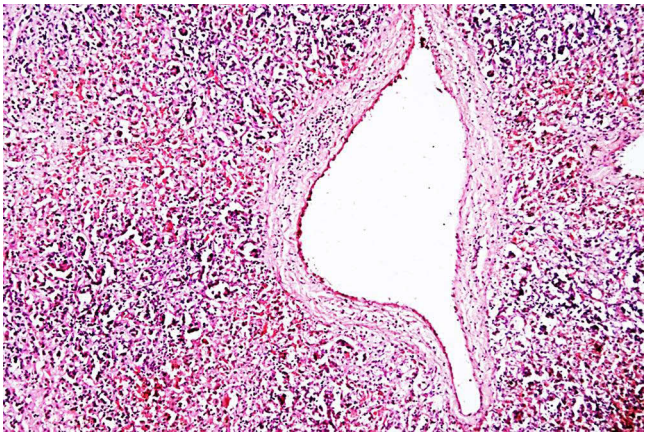

Figure 1 Violations of architectonics, areas of dystrophic hepatocytes separated by fields of proliferating bile ducts, most of which are in the form of tubular structures. Hemorrhage foci. Pronounced inflammatory infiltration. G.E. x 40.

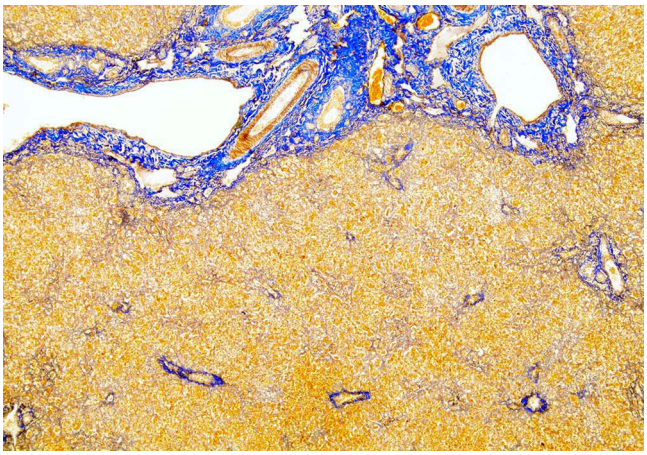

Figure 2 Portal fibrosis. Trichrome Azan.x 20.

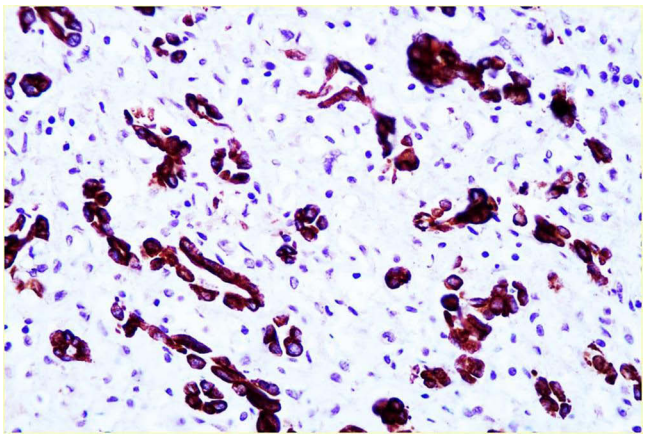

Figure 3 CK 7 (cytokeratin) ductular proliferation, with the formation of functionally incapable ducts, they are narrow and filled with proliferating or destructive epithelium (x20).

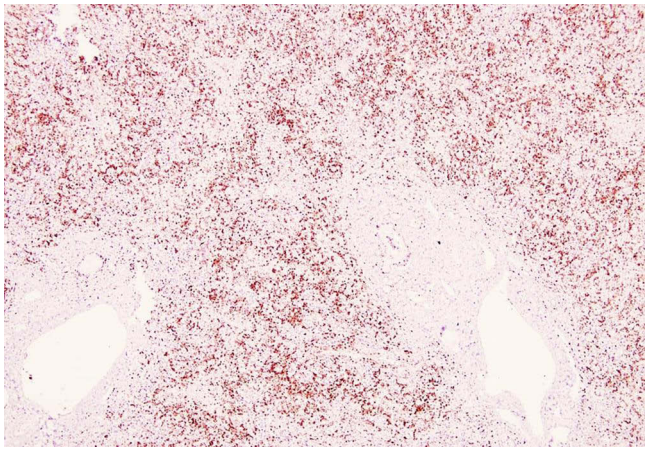

Figure 4 Expression of CD45 in the cells of inflammatory polymorphic cellular infiltrate (x20).

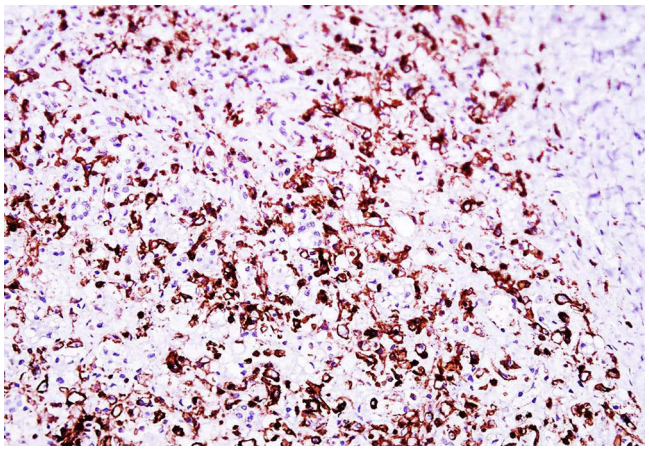

Figure 5 Expression of CD68 in cells of the macrophage line (x40).

Discussion

This case is interesting because three competing diseases were found in this patient, each of which individually or in combination could have provoked the development of ALF.

Viral hepatitis A is a widespread disease in the world with a mostly benign and self-limiting course. This case reflects a rare variant of the malignant course of HAV with the development of ALF. It should be noted that the onset of the disease was typical for viral hepatitis A, and the patient's previous medical history did not contain data on possible concomitant pathology or conditions that could be the basis of the adverse course of the disease. It is known that viral hepatitis A infection can cause fulminant hepatitis. It is believed that about 1% of cases of viral hepatitis A are accompanied by the development of ALF.[2] The causes of ALF progression are still unclear. Among the published studies there are data that indicate that immunological response mechanisms, in particular those caused by cytolytic T cells, can play an important role in liver damage; in addition, there is an observation that an unfavorable prognosis is associated with a rapid decrease in the viral load in the acute period of the disease, the presence of chronic liver disease.[11–13] Morphological changes in the liver in ALF against the background of viral hepatitis A are characterized by diffuse necroinflammatory changes that cover both lobules and periportal areas, disorganization of lobules, balloon dystrophy, apoptosis, and ductular reaction.[10,14] Such changes were noted during the pathohistological examination of this patient.

In this patient, in addition to the marker of the acute phase of viral hepatitis A, a positive test for IgM to EBV was also detected, which indicates an acute period of this infection. It is known that EBV infection is often associated with liver

damage, but in the vast majority of patients it is subclinical and self-limited, manifested by a transient and mild increase in transaminases. Usually, liver damage occurs against the background of symptoms of infectious mononucleosis, but liver damage can also occur in isolation. The histological picture of EBV hepatitis is characterized by sinusoidal lymphocytic infiltration, which resembles strings of beads. The presence of atypical mononuclear cells is often noted.[15] Severe liver damage is rare and occurs mainly against the background of immune deficiency, although there are also cases of hepatitis with the development of ALF in immunocompetent individuals.[16,17] In this patient, the previous medical history did not contain data on possible immune suppression, and the clinical picture did not have symptoms characteristic of infectious mononucleosis. Pathohistological examination in the future also did not reveal changes characteristic of EBV infection. In our opinion, taking into account the clinical picture and morphological changes, in this case, EBV infection did not play a leading role in liver damage, and the predominant influence here was due to the hepatitis A virus. The possibility of a co-infection factor and the combined influence of HAV and EBV is also not excluded. At the time of writing, we did not find in the available literature any generalized or systematized information regarding the course of HAV and EBV co-infection and how they together may affect the severity of hepatitis. Single reports testify to the favorable course of such cases.[18,19] We found no published cases of ALF caused by HAV and EBV co-infection.

In addition to diffuse necrotic changes typical for fulminant hepatitis, histological examination revealed marked portal fibrosis and neoductal proliferation. Active ductular proliferation was also confirmed by immunohistochemical examination for cytokeratin 7. These findings, together with manifestations of peribiliary macrophage and lymphocytic infiltration, allowed the patient to be diagnosed with autoimmune sclerosing cholangitis (ASC). This disease is a cross syndrome, which is manifested by immunological, clinical and histological signs of both autoimmune hepatitis and primary sclerosing cholangitis.[20] It is a chronic inflammatory disease of unknown etiology that affects the intrahepatic and/or extrahepatic bile ducts, leading to their damage and progressive liver fibrosis. According to the results of a 21-year prospective cohort study by Hercun et al, of 32 childhood patients diagnosed with autoimmune sclerosing cholangitis and primary sclerosing cholangitis, 69% had concomitant autoimmune intestinal disease, 5 (12.5%) required liver transplantation, 11 (27 0.5%) had a diagnosis of liver cirrhosis, and 8 (20%) had an episode of acute cholangitis.[21] The typical picture of the disease is characterized by a gradually progressive course, but in the literature there are also descriptions of cases of ALF caused by ASC.[22,23] In the clinical case that we are considering, the child's previous medical history did not contain any data that would testify in favor of damage to the liver and biliary tract. And the histological picture revealed changes in the level of fibrosis. This gives reason to believe that the course of ACS was subclinical. However, scientific data show that even minor chronic liver diseases can provoke an adverse course of viral hepatitis A.[11] In our opinion, exactly this course of events took place and the development of ALF with viral hepatitis A was facilitated by the presence of autoimmune sclerosing cholangitis in the child.

Conclusion

The case is novel as regards the occurrence of two viral hepatitis with different modes of transmission on a background of unidentified liver disease.

Ethical Approval

Ethical approval is not required to publish the case details in accordance with local or national guidelines.

Consent for Publication

Written informed consent was obtained from the parents of the minor patient, including for the publication of the article and its content.

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Disclosure

The author declares no conflicts of interest in this work.

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