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# PATHOMORPHOLOGICAL CHANGES IN THE LIVER CAUSED BY HEPATITIS B, C, B+C VIRUSES IN THE DECEASED HIV-INFECTED PERSONS

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*Pathohistological peculiarities of liver histological preparations of 75 HIV-infected deceased people with chronic viral hepatitis which diagnosed during their life: hepatitis B was in 8, C – in 24, B+C – in 43 patients. It was determined that in all patients (100.0 %), with any type of chronic hepatitis (B, C or B+C) there was a lymphocyte-macrophage infiltration of portal tracts and stroma. In persons with hepatitis B there were a focal and periportal necrosis of hepatocytes in 100.0 % of patients, hydropic dystrophy of hepatocytes - in 87.5 % and liver cirrhosis - in 25.0 %. In patients with hepatitis C a fatty dystrophy of the liver was found in 91.7 % that more often than in patients with hepatitis B (12.5 %, p<0.001), the focal periportal necrosis of hepatocytes was less (12.5 % vs. 100.0 %, respectively, p<0.001) and liver cirrhosis was in 41.7 %.*

*In patients with hepatitis B+C, the liver tissue included signs characteristic of both hepatitis B and C: a hydropic dystrophy (69.8 %), fatty dystrophy (30.2 %), periportal bridging necrosis (51.2 %), liver fibrosis (34.9 %). As a result of these complex pathological processes in the liver, a cirrhosis was found more often than in other groups of patients (67.4 % vs. 41.7 % of patients with hepatitis C, p=0.041, and vs. 25.0 % of patients with hepatitis B, p=0.024). Histology activity index of hepatitis and stage of liver fibrosis according to Knodell R.G. (1981) did not differ in frequency in all groups of patients. In all patients a strong negative correlation was found between them (r=-0.607, p<0.001). This finding reflects a decrease in the histological activity of hepatitis against the background of increased fibrotic changes in the body.*

***Conclusion.*** *It has been found that the hydropic dystrophy and focal intralobular and periportal bridging necrosis of hepatocytes are characteristic of hepatitis B infection in HIV-infected deceased persons. Hepatitis C is characterized by the fatty dystrophy and cirrhosis of the liver. The presence of hepatitis B+C causes the liver changes characteristic of both hepatitis B and C simultaneously: the hydropic dystrophy, fatty dystrophy, necrosis of hepatocytes. The liver cirrhosis is most often present in patients with hepatitis B+C. The degree of liver fibrosis negatively correlated with the histology activity index of hepatitis.*

***Key words:*** *immunodeficiency; viral infection; hepatitis; liver fibrosis; liver cirrhosis.*

HIV-infection and viral hepatitis B (HBV) and C (HCV) constitute one of the biggest problems of medicine, and their spread is facilitated by common ways and factors of transmission [1-4].

According to estimated data, as of January 1, 2019, 5 % (2,107,660) of people in Ukraine are infected with HCV, of which 29,946 are co-infected with HCV and the human immunodeficiency virus (HIV), 3.6 % (1,517,515) of people have chronic hepatitis C, and 1.5 % (632,298) of people are infected with HBV, of which 5,640 are co-infected with HBV and HIV [5]. By the end of 2021, according to the results of screening studies, the number of HIV-infected people (PLWHIV) are co-infected HCV was 27,913 and there were 4,770 PLWHIV infected with HBV, including 3,004 PLWHIV with HCV and HBV co-infection. [6].

At the same time, some scientists claim that liver damage is a characteristic peculiarity of immunodeficiency caused by HIV, which itself has certain hepatotropic properties [7]. Lifelong antiretroviral therapy is also accompanied by hepatotoxic side effects and, in the presence of comorbid viral hepatitis, can negatively affect the functional state of the liver [8]. Late diagnostics and treatment of HIV-infection and opportunistic diseases also worsen the functional state of the organ and worsen the patient's prognosis [9]. The risk of mortality among patients with HIV/HBV and HIV/HCV co-infection is 1.6-fold higher than in patients with HIV mono-infection, and in triple infection with HIV/HBV/HCV – 2.29-fold higher [10].

The morphogenesis of chronic viral hepatitis is considered from the point of view of three interrelated components: 1) hepatocyte damage resulting in dystrophy with subsequent development of hepatocyte necrosis; 2) cellular infiltration, which is the reaction of immunocompetent cells to a viral infection; 3) liver fibrosis, as the terminal result of a complex of destructive-proliferative processes [11]. HIV/HBV/HCV individuals had higher rates of end-stage liver disease compared with those with HIV/HCV and HIV/HBV [12, 13].

A detailed comparative analysis of morphological changes in the liver of HIV-infected patients caused by hepatitis B, C, B+C viruses would help to understand their contribution to the development of the end-stage liver disease, and to find new ways to influence the course and progression of the disease. All this is very important, especially for patients from Precarpation region, who are characterized by their own set of behavioral and biological risk factors.

To study and compare histopathological peculiarities of the liver in HIV-infected deceased persons with clinically verified hepatitis B, C and B+C.

## Patients and methods

A retrospective analysis of 75 autopsies of HIV-infected patients with clinically verified damage with the hepatitis B, C, B+C virus was conducted on the basis of the Pathology Department of the Ivano-Frankivsk Regional Clinical Hospital, for the period of 2009–2018.

The age of the deceased patients was 25-60 years, on average – 38.34±0.79 years; men predominated among them – 57 (76.0 %), and there were 18 (24.0 %) women; clinical stage III of HIV-infection was diagnosed in 3 (4.0 %) and stage IV – in 72 (96.0 %) patients. The group of patients with a clinical diagnosis of “chronic hepatitis B” consisted of 8 people, hepatitis C – 24, and B+C – 43 people.

The etiology of liver damage caused by hepatotropic viruses in patients was verified in vivo by clinical and serological methods and was obtained from the patient’s medical record. Information about comorbidities was also taken from the patient’s medical record. Pathomorphological changes of the liver were studied in histological preparations in these three groups of patients, and then they were compared with each other. Classical histological research methods of study with hematoxylin and eosin staining of preparations, as well as Masson’s trichrome staining for the detection of collagenous fibers and Hart’s staining for the detection of elastic fibers, were used in the work [14].

The histology activity index (HAI) of the inflammatory process in the liver was determined depending on the presence and severity of hepatocyte necrosis, intralobular dystrophy and portal inflammation, as well as the stage of liver fibrosis according to Knodell R.G. et al. (1981). Histological preparations were examined using an optical system for obtaining microscopic images (a Leica DME microscope, a “Nikon P5100” digital camera, an optical nozzle developed at the Department of Pathological Anatomy of the Ivano-Frankivsk National Medical University) [15].

The study was approved by the Ethics Committee of the Ivano-Frankivsk National Medical University (Potocol № 109/19 dated May 29, 2019).

All statistical analyses were carried out using the IBM SPSS Statistics 26.0 software package. For comparison between the groups the independent samples and $\chi^2$ test were performed. Cramer’s V correlation test was used to examine the association between the histology activity index of hepatitis and the stage of liver fibrosis. A p-value of less than 0.05 was considered statistically significant.

## Research results

The deceased HIV-infected patients (N=75) were divided into 3 groups, depending on the etiological factor of liver damage: the group of patients with a clinical diagnosis of chronic hepatitis B consisted of 8 people, hepatitis C – 24, and hepatitis B+C – 43. Demografic, comorbidity characteristics and causes of death of patients are presented in Table 1.

Table 1

Comparison of demografic, comorbidity characteristics and causes of death of HIV-infected patients with hepatitis B, C, B+C, n=75

| Parameters | Hepatitis B n=8 | Hepatitis C n=24 | Hepatitis B+C n=43 | p-value |
|---|---|---|---|---|
| Age (years), mean±SD | 43.13±8.01 | 37.08±6.85 | 38.16±6.46 | 0.094 |
| Gender, n (%)<br>Male<br>Female | <br>3 (38.0)<br>5 (62.0) | <br>19 (79.0)<br>5 (21.0) | <br>35 (81.0)<br>8 (19.0) | <br><0.05<br><0.05 |
| HIV-infection, stage, n (%)<br>III<br>IV | <br>0 (0)<br>8 (100.0) | <br>0 (0)<br>24 (100.0) | <br>3 (7.0)<br>40 (93.0) | <br><br>0.679 |

Continuation of the table 1

| Parameters | Hepatitis B n=8 | Hepatitis C n=24 | Hepatitis B+C n=43 | p-value |
|---|---|---|---|---|
| Comorbidities, opportunistic infections, n (%) | | | | |
| Meningitis and meningoencephalitis of various etiology | 4 (50.0) | 12 (50.0) | 17 (39.5) | 0.698 |
| Polyfocal leukoencephalopathy | 1 (12.5) | 0 (0) | 0 (0) | |
| Pulmonary tuberculosis and extrapulmonary tuberculosis | 5 (62.5) | 12 (50.0) | 25 (58.1) | 0.787 |
| Pneumocystis pneumonia | 1 (12.5) | 2 (8.3 ) | 0 (0) | 0.091 |
| Bacterial pneumonia with abscess | 0 (0) | 6 (25.0) | 10 (23.2) | 0.385 |
| Oropharyngeal candidiasis, esophagus | 3 (37.5) | 14 (38.3) | 26 (60.5) | 0.522 |
| Liver cirrhosis | 2 (25.0) | 11 (45.8) | 28 (65.2) | 0.066 |
| Psychic and behavioral disorders due to alcohol use (APBD) | 2 (25.0) | 3 (12.5) | 5 (11.6) | 0.540 |
| Opiate-related psychic and behavioral disorders (OPBD) | 2 (25.0) | 12 (50.0) | 20 (46.5) | 0.468 |
| Kaposi's sarcoma | 0 (0) | 1 (4.1) | 0 (0) | |
| Lung cancer | 0 (0) | 1 (4.1) | 0 (0) | |
| Hodgkin's lymphoma | 0 (0) | 0 (0) | 1 (2.3) | |
| Pancreatic cancer | 0 (0) | 0 (0) | 1 (2.3) | |
| The immediate causes of death, n (%) | | | | |
| Multiple organ failure | 3 (37.5) | 14 (58.3) | 13 (30.2) | 0.075 |
| Cerebral edema with wedging into the Large occipital foramen | 3 (37.5) | 10 (41.6) | 19 (44.2) | 0.944 |
| Pulmonary edema | 2 (25.0 ) | 15 (62.5) | 22 (51.2) | 0.165 |
| Pulmonary heart failure | 2 (25.0 ) | 0 (0) | 3 (7.0) | 0.057 |
| Hepatocellular failure | 1 (12.5) | 0 (0) | 0 (0) | |
| Liver cirrhosis | 1 (12.5) | 7 (29.1) | 14 (32.5) | 0.656 |

Differences in the frequency of extrahepatic pathology, opportunistic infections, were insignificant (p>0.05), so they were evenly distributed in groups of patients with clinically verified chronic hepatitis of different viral etiology (Table 1). Cirrhosis of the liver, as a cause of death, tends to dominate when infected with the B+C hepatitis virus (32.5 % against 29.1 % (p>0.05) and 12.5 % (p>0.05), respectively.

During the pathomorphological evaluation of the inflammatory process in the liver, Histology activity index (HAI) was the same in different groups of patients independently from type of viruses. Minimal activity (A1) was determined in 25.0 % of patients with clinically verified chronic hepatitis B; in 37.5 % with hepatitis C, and tend to be more in people with hepatitis B+C viruses – 53.5 % ($p_1$=0.131) (Table 2). At the same time, intralobular dystrophy and focal necrosis of hepatocytes were detected in less than in 1/3 of the lobules, as well as the slight portal inflammation was also observed (single lymphocytic cells in 1/3 of the portal tracts) (Fig. 1).

Mild activity (A2) was observed in the clinically verified hepatitis B – in 37.5 %, C – in 25.0 %, B+C – in 23.3 % of cases with a similar frequency (p>0.05) (Table 2). It was characterized by dystrophy and graded small focal necrosis of hepatocytes in 1/3 of the lobules, as well as a moderate increase in the number of inflammatory cells in 1/3 of the portal tracts) (Fig. 2, Fig. 3).

Table 2

Histology activity index in the deceased HIV-infected persons with hepatitis B, C, B+C

| Knodell HAI | Hepatitis B n=8, (%) | Hepatitis C n=24, (%) | Hepatitis B+C n=43, (%) | p-value |
|---|---|---|---|---|
| A1 (0-3) | 2 (25.0) | 9 (37.5) | 23 (53.5) | $p_1$=0.131<br>$p_2$=0.210<br>$p_3$=0.520 |
| A2 (4-8) | 3 (37.5) | 6 (25.0) | 10 (23.3) | $p_1$=0.396<br>$p_2$=0.873<br>$p_3$=0.496 |
| A3 (9-12) | 2 (25.0) | 5 (20.8) | 8 (18.6) | $p_1$=0.676<br>$p_2$=0.825<br>$p_3$=0.805 |
| A4 (13-18) | 1 (12.5) | 4 (16.7) | 2 (4.6) | $p_1$=0.387<br>$p_2$=0.099<br>$p_3$=0.779 |

Notes: $p_1$ – reliability of the difference between indices in groups of patients with hepatitis B+C and hepatitis B; $p_2$ – reliability of the difference between indices in the group of patients with hepatitis B+C and hepatitis C; $p_3$ – reliability of the difference between indices in the group of patients with hepatitis C and hepatitis B.

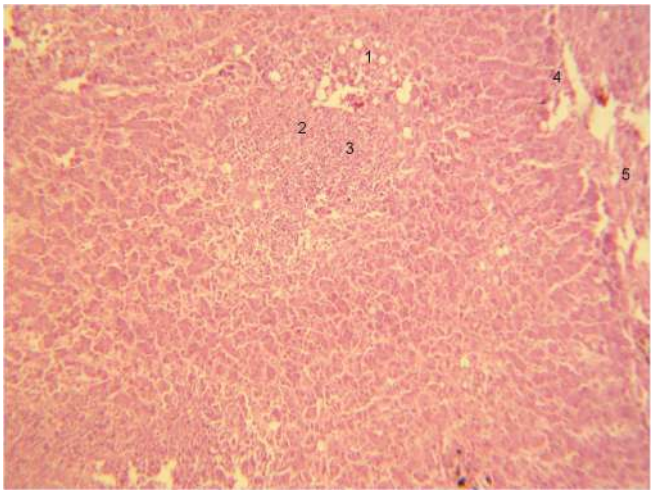


Fig. 1. Pathomorphological picture of the liver in a deceased HIV-infected patient with the accompanying clinically verified chronic hepatitis C, minimal activity of the inflammatory process (A1), minimal portal fibrosis (F1).
Small-focal large-droplet fatty dystrophy of hepatocytes (1), focal intralobular necrosis of hepatocytes (2) with lymphocyte-macrophagic infiltration (3), minimal infiltration of lymphocytes in the portal tracts (4), minimal portal fibrosis (5).
Staining: hematoxylin and eosin. Magnification: 20x.

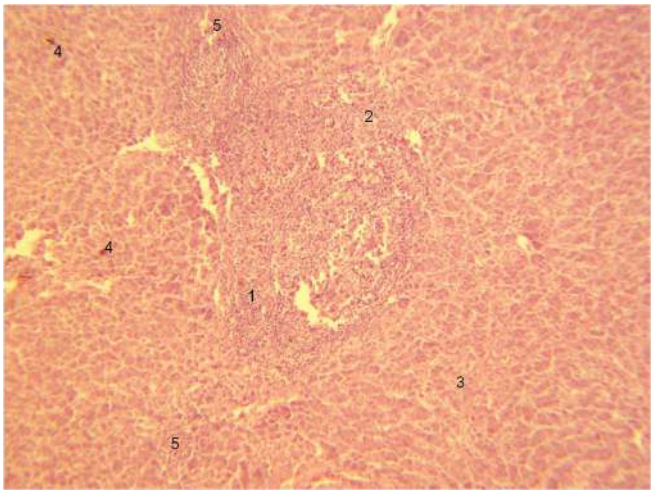


Fig. 2. Pathomorphological picture of the liver in a deceased HIV-infected patient with concomitant clinically verified chronic hepatitis B, low activity of the inflammatory process (A2), portal fibrosis with single periportal septa (F2).
Mild infiltration of the portal tract with lymphocytes and macrophages (1), necrosis of hepatocytes in the border plate zone (2), minimal hydropic focal dystrophy of hepatocytes (3), focal cholestasis (4), portal fibrosis with single portal septa (5).
Staining: hematoxylin and eosin. Magnification: 20x.

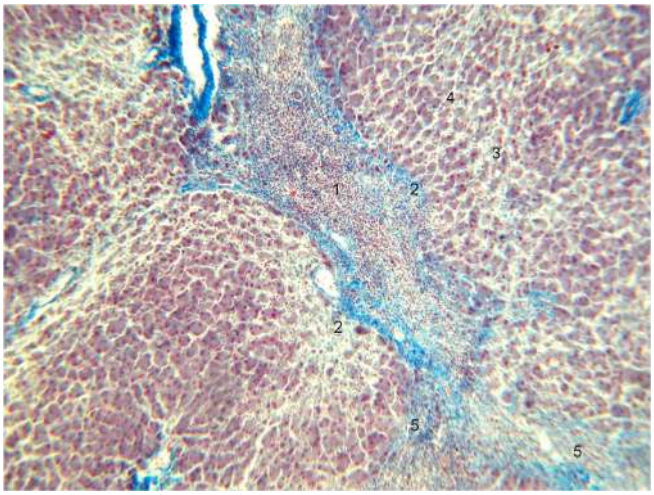


Fig. 3. Pathomorphological picture of the liver in a deceased HIV-infected patient with concomitant clinically verified chronic hepatitis B, low activity of the inflammatory process (A2), portal fibrosis with single periportal septa (F2).
Mild infiltration of the portal tract with lymphocytes and macrophages (1), necrosis of hepatocytes in the border plate zone (2), minimal hydropic focal dystrophy of hepatocytes (3), intralobular slight inflammatory cellular infiltration (4), portal fibrosis with single portal septa (5).
Staining: according to Masson. Magnification: 20x.

Moderate activity (A3) was detected in 25.0 % of patients with hepatitis B, in 20.8 % of patients with hepatitis C and in 18.6 % with hepatitis B+C with a comparable frequency in all three groups ($p>0.05$) (Table 2). Moderate bridging necrosis of hepatocytes (<50 % of the circumference of most portal tracts) was noticeable; 2/3 of the portal tracts were moderately infiltrated with the inflammatory cells, and dystrophically changed hepatocytes were in 1/3-2/3 of the lobules (Fig. 4).

Councilman bodies (hepatocytes in a state of apoptosis) were found mainly around the central vein. Some cells had strongly vacuolated cytoplasm and pyknotically altered nuclei, which reflected the development of colliquative necrosis. The presence of necrotized hepatocytes indicated the pronounced activity and progression of hepatitis, they were mainly located periportally.

Severe activity (A4) was determined in 12.5 % of patients with hepatitis B, in 16.7 % – with hepatitis C, and the least was in patients with hepatitis B+C – 4.7 %. At the same time, there is a statistical difference in the frequency of A1 and A4 in patients with hepatitis B+C (53.5 % against 4.7 %, $p<0.001$) (Table 2). In liver preparations, massive bridging and multilobular necrosis were found in >50 % of lobules. More than 2/3 of the lobules had hepatocyte dystrophy, as well as the pronounced portal inflammation

manifested by the dense location of inflammatory cells in 2/3 or more of the portal tracts.

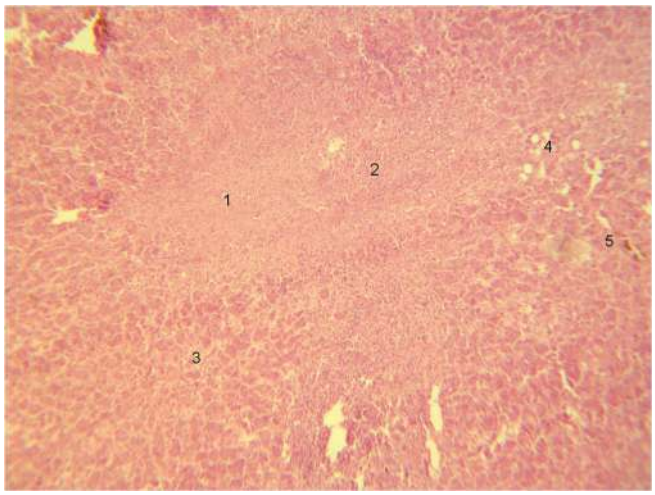


Fig. 4. Pathomorphological picture of the liver in a deceased HIV-infected patient with the concomitant clinically verified chronic hepatitis B+C, moderate activity of the inflammatory process (A3), minimal portal fibrosis (F1).
Moderate periportal necrosis of hepatocytes (1) with moderate lymphohistiocytic infiltration (2), focal hydropic (3) and fatty (4) dystrophy of hepatocytes, slight portal fibrosis (5).
Staining: hematoxylin and eosin. Magnification: 20x.

When comparing the distribution of the activity levels in patients with different clinically determined diagnoses of viral hepatitis, a relatively uniform distribution of activity frequencies of A1, A2, A3, and A4 can be noted in patients with hepatitis B and C (Table 2). An exception is the group of patients with hepatitis B+C, where there is a significant difference between the frequencies of A1 53.5 % and A4 – 4.7 % (p<0.001) (Table 2). This fact can be explained by the attenuation of the activity of the inflammatory process against the background of the rapid development of cirrhotic changes in the liver in these patients.

A comparison of the prevalence of pathohistological changes in three groups of the deceased HIV-infected patients revealed that cellular infiltration of the periportal tracts of the liver was characteristic of all patients regardless of the etiology of chronic hepatitis (100 %). However, its peculiarities, as well as the nature of hepatocyte dystrophy and necrosis, have differed. Thus, in patients who were diagnosed with chronic hepatitis B during life, lymphocyte-macrophage cell infiltration occurred, which was associated with hydropic dystrophy of hepatocytes in 87.5 % of patients and with the necrosis of hepatocytes in 100 %. Necrosis was mainly periportal (87.5 %) and less often intralobular (12.5 %) (Table 3) (Fig. 2, Fig. 3). Periportal necrosis was observed ten times more often than in patients with hepatitis C (87.5 % against 8.3 %, respectively, $p_3$<0.001).

In patients with clinically verified hepatitis C, the inflammatory cellular infiltration had a diffuse lymphocytic character with infiltration of portal tracts, here and there with clusters and the formation of lymphoid follicles. Fatty dystrophy of the liver (91.7 %) was a characteristic feature of hepatitis C. First of all, fine-droplet fatty dystrophy of hepatocytes (79.2 %) and, less often, large-droplet one (12.5 %), was observed (Fig. 1), (Table 3). In patients with hepatitis C, compared to persons with hepatitis B, fatty dystrophy has absolutely prevailed (91.7 % against 12.5 %, respectively, p<0.001), and hydropic dystrophy was relatively insignificant (8.3 % against 87.5 %, respectively, $p_3$<0.001).

Table 3

Histological characteristics of changes in the liver in the deceased HIV-infected persons with hepatitis B, C, B+C

| Pathomorphological changes | Hepatitis B n=8, (%) | Hepatitis C n=24, (%) | Hepatitis B+C n=43, (%) | p-value |
|---|---|---|---|---|
| Hydropic dystrophy of hepatocytes | 7 (87.5) | 2 (8.3) | 30 (69.8) | $p_1$=0.303<br>$p_2$<0.001<br>$p_3$<0.001 |
| Fatty dystrophy of hepatocytes: | 1 (12.5) | 22 (91.7) | 13 (30.2) | $p_1$=0.303<br>$p_2$<0.001<br>$p_3$<0.001 |
| • fine-droplet | 1 (12.5) | 19 (79.2) | 10 (23.3) | $p_1$=0.498<br>$p_2$<0.001<br>$p_3$<0.001 |
| • large-droplet | 0 (0.0) | 3 (12.5) | 3 (7.0) | $p_1$<0.001<br>$p_2$=0.442<br>$p_3$=0.294 |
| Hepatocyte necrosis: | 8 (100.0) | 3 (12.5) | 32 (74.4) | $p_1$>0.05<br>$p_2$<0.001<br>$p_3$<0.001 |
| • periportal bridging | 7 (87.5) | 2 (8.3) | 22 (51.2) | $p_1$=0.057<br>$p_2$<0.001<br>$p_3$<0.001 |
| • focal intralobular | 1 (12.5) | 1 (4.2) | 10 (23.3) | $p_1$=0.498<br>$p_2$=0.044<br>$p_3$=0.400 |

Notes: $p_1$ – reliability of the difference between indices in groups of patients with hepatitis B+C and hepatitis B; $p_2$ – reliability of the difference between indices in the group of patients with hepatitis B+C and hepatitis C; $p_3$ – reliability of the difference between indices in the group of patients with hepatitis C and hepatitis B.

Inflammatory infiltration of the stroma and portal tracts in patients with clinically diagnosed hepatitis B+C was lymphocytic-macrophagic in nature, similar to patients with hepatitis B. At the same time, a significant number of patients (69.8 %) had marked dystrophy of hepatocytes of a hydropic nature, similar to hepatitis infection B and with the same frequency (87.5 %, respectively, $p_1$=0.303). Fatty dystrophy of hepatocytes (fine-droplet and large-droplet dystrophy) was also observed, which was characteristic of hepatitis C, but its frequency was three times lower (30.2 % against 91.7 %, respectively, p<0.001). The frequency of necrosis of hepatocytes (both periportal and intralobular) was comparable to the group of patients with hepatitis B (74.4 % against 100.0 %, respectively, p>0.05) and significantly exceeded the frequency in the presence of only hepatitis C, 74.4 % against 12.5 %, respectively, $p_2$<0.001). However, in patients with hepatitis B+C, small focal necrosis of liver cells prevailed, which corresponded to minimal and insignificant activity of the inflammatory process.

Stages of liver fibrosis in the studied groups were determined according to Knodell R.G. (1981) in preparations stained according to Masson. Stage F0, in which there are no signs of fibrosis, was found in HIV-infected persons with a clinical diagnosis of hepatitis B and C in 25.0 % and 16.7 % of cases, respectively (Table 4). In clinically verified hepatitis B+C, stage F0 was not found in any case and it was associated with more intense fibrosis formation in this group of patients compared to others.

Table 4

Stages of liver fibrosis according to Knodell R.G. (1981) in the deceased HIV-infected persons with hepatitis B, C, B+C

| Stages of fibrosis | Hepatitis B n=8, (%) | Hepatitis C n=24, (%) | Hepatitis B+C n=43, (%) | p-value |
|---|---|---|---|---|
| F0 | 2 (25.0) | 4 (16.7) | 0 (0.0) | $p_1$<0.001<br>$p_2$=0.006<br>$p_3$=0.601 |
| F1 | 1 (12.5) | 3 (12.5) | 2 (4.7) | $p_1$=0.387<br>$p_2$=0.242<br>$p_3$=1.000 |
| F2 | 2 (25.0) | 4 (16.7) | 6 (14.0) | $p_1$=0.431<br>$p_2$=0.766<br>$p_3$=0.601 |
| F3 | 1 (12.5) | 3 (12.5) | 6 (14.0) | $p_1$=0.913<br>$p_2$=0.868<br>$p_3$=1.000 |
| F4 (liver cirrhosis) | 2 (25.0) | 10 (41.7) | 29 (67.4) | $p_1$=0.024<br>$p_2$=0.041<br>$p_3$=0.400 |

Notes: $p_1$ – reliability of the difference between indices in groups of patients with hepatitis B+C and hepatitis B; $p_2$ – reliability of the difference between indices in the group of patients with hepatitis B+C and hepatitis C; $p_3$ – reliability of the difference between indices in the group of patients with hepatitis C and hepatitis B.

Stage F1, in which fibrotic expansion of the portal tracts without the formation of septa was observed. Along with the collagenous fibers, the presence of elastic fibers was noted when staining histological preparations according to Hart (Fig. 5).

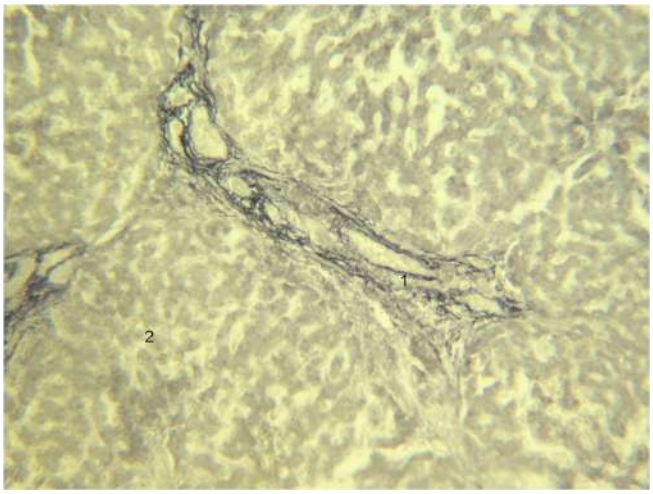


Fig. 5. Pathomorphological picture of the liver of a deceased HIV-infected patient with hepatitis C virus damage, minimal inflammatory activity (A1), slight portal fibrosis (F1).
Elastic fibers in the portal field (1), fatty dystrophy of hepatocytes (2).
Staining: according to Hart (elastic fibers of black staining). Magnification: 20x.

With the development of the pathological process, portal fibrosis with single porto-portal septa is formed at the stage F2 (Fig. 6), which was determined in hepatitis B – in 25.0 % of patients, in hepatitis C – in 16.7 %, and in B+C – in 14.0 % of patients.

With the progression of fibrosis into the stage F3, gradual growth of connective tissue was observed in the preparations in the portal tracts and in the parenchyma of the lobules at the site of necrotized hepatocytes with the formation of multiple porto-portal, porto-central septa, in hepatitis B and C – in 12.5 % of cases, and in B+C – in 14.0 % of cases, while pathomorphological features of background hepatitis remained (Fig. 7, Fig. 8). At the same time, active proliferation of intrahepatic bile ducts was noted, often in combination with periductular fibrosis outside the hepatic triad.

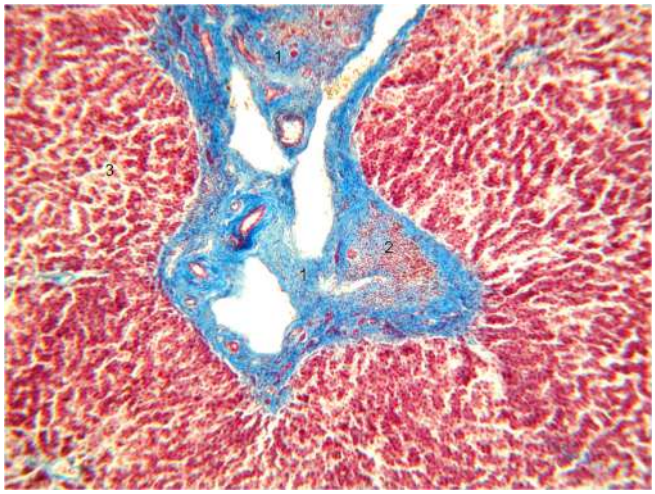

Fig. 6. Pathomorphological picture of the liver of the deceased HIV-infected patient with hepatitis B virus damage, minimal inflammatory activity (A1), moderate portal fibrosis with a tendency to the formation of periportal septa (F2).
Collagenous fibers in the portal field (1), slight portal infiltration by lymphocytes and macrophages (2), minimal small focal hydropic dystrophy of hepatocytes (3).
Staining: according to Masson (collagenous fibers are blue). Magnification: 20x.

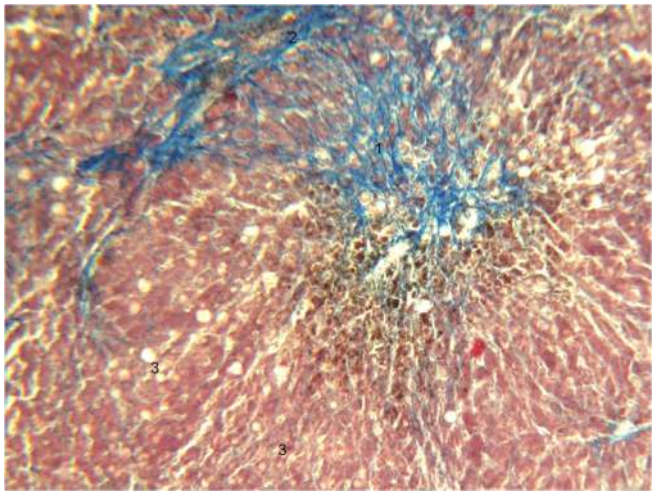

Fig. 7. Intralobular fibrosis of the liver in clinically verified chronic hepatitis B+C in the deceased HIV-infected patient.
Intralobular fibrosis (1), centro-portal connective tissue septa (2), diffuse large- and fine-droplet fatty dystrophy (3).
Staining: according to Masson. Magnification: 20x.

The architecture of liver lobules was changed in patients with cirrhosis (F4), pseudolobules were formed between massive multidirectional bundles of the collagenous fibers, which can be seen by the blue color in the preparation. At the same time, pronounced angiomatosis of the stroma was observed – the sprouting of blood vessels in the thickness of collagenous fibers, which provided these pseudoparticles with blood supply (Fig. 9). Such changes corresponded to the definition of liver cirrhosis and were most often found in patients with clinically verified chronic hepatitis B+C (67.4 %), less often in patients with hepatitis C (41.7 %, $p_2$=0.041) and hepatitis B (25.0 %, $p_1$=0.024) (Table 4).

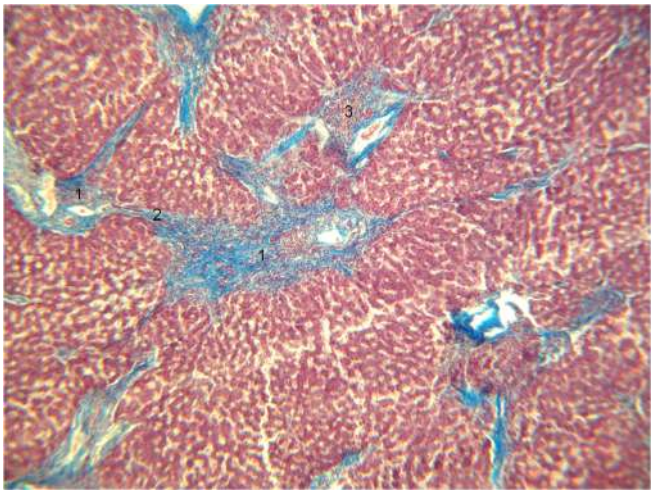

Fig. 8. Periportal liver fibrosis (F3) in clinically diagnosed chronic hepatitis B+C in the deceased HIV-infected patient.
Portal fibrosis (1), periportal connective tissue septa (2), slight lymphohistiocytic infiltration of portal tracts (3)
Staining: according to Masson. Magnification: 20x.

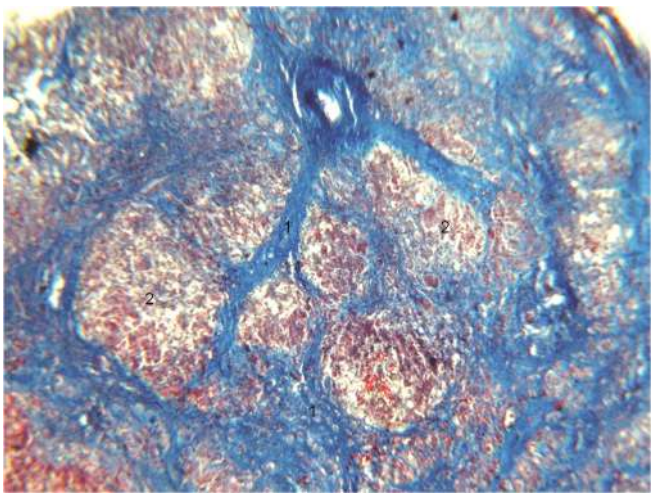

Fig. 9. Porto-portal, porto-central, centro-central connective tissue cords with the formation of pseudoparticles (F4) in viral liver cirrhosis B+C in the deceased HIV-infected patient.
Growth of collagenous fibers (1), pseudoparticles (2).
Staining: according to Masson. Magnification: 20x.

When evaluating the relationship between Histology activity index according to Knodell R.G. (Knodell HAI) and stages of liver fibrosis according to Knodel R.G. in HIV-infected patients affected by hepatitis viruses, was found to be negatively correlated in all groups of the patients (Table 5).

Table 5

Correlation analysis between Knodell HAI and stages of liver fibrosis in the deceased HIV-infected persons with hepatitis B, C, B+C

| | r | p-value |
|---|---|---|
| Hepatitis B (n=8) | -1.000 | 0.007 |
| Hepatitis C (n=24) | -0.835 | <0.001 |
| Hepatitis B+C (n=43) | -0.876 | <0.001 |
| All cases (N=75) | -0.607 | <0.001 |

Notes: r – Cramer's V test;

The correlation coefficients between Knodell HAI in the liver and the stage of liver fibrosis in each group of patients were comparable: in patients with clinically verified hepatitis B: r = -1.000 (p=0.007); in the group of patients with hepatitis C: r = -0.835 (p<0.001); in the group of patients with hepatitis B+C: r = -0.876 (p<0.001). These relationships indicate that HAI decreases against background the stage of liver fibrosis increases, regardless of the etiology of hepatitis.

As a result of the research performed, pathohistological peculiarities of the liver were found in the deceased HIV-infected persons; these peculiarities characterize groups of patients with clinically verified comorbid hepatitis B, C, B+C. Thus, in chronic hepatitis B diagnosed during life, hydropic dystrophy prevails (87.5 %); this becomes the main cause of bridging tiny periportal necrosis of hepatocytes. These pathological processes lead to the formation and progression of fibrosis in 50.0 % of people and liver cirrhosis in a relatively small number of patients (25.0 %). In the studies of Singh K.P. et al. (2022) suggested that liver fibrosis in HIV/HBV is triggered by increased hepatocyte apoptosis, microbial translocation and/or HIV/HBV viral products. Sera from people with HIV and HBV coinfection have an enhanced capacity to activate primary human hepatic stellate cells (hHSC). They identified an increase in circulating of the alarmin high mobility group box 1 (HMGB1) which, in addition to HIV-gp120 and translocated microbial products, drove pro-fibrogenic changes in hHSC, as mechanisms contributing to accelerated liver disease in HIV/HBV [16]. Liver damage in chronic hepatitis B, as a rule, intensifies with the immunodeficiency increase [17].

We've determined that in HIV-infected patients with the concomitant chronic hepatitis C against the background of inflammatory infiltration of the stroma, intense lipid infiltration of hepatocytes (79.2 %) and fibrosis formation (37.5 %) with the development of liver cirrhosis (in 41.7 % of patients) prevail. These data are consistent with the results of a morphological study performed by Marks K. M. et al. (2005), where the relationship between the severity of steatosis and periportal liver fibrosis in HIV-infected patients with HCV-infection was shown [18]. Such structural changes in the parenchyma are correlated with HCV replication indices, which gives reason to consider a violation of lipid metabolism in the cell as virus-induced one, which contributes to the further effective production of active virions [19]. The majority of people with clinically diagnosed hepatitis C (83.3 %) had lymphocytic infiltration of portal tracts and interlobular septa, which in some places form lymphoid follicles, which is also considered a pathognomonic sign of chronic hepatitis C. A multivariate logistic regression performed in the HIV/HCV group revealed that relatively older patient's age, CD4+ count <200 cells/mm$^3$, type 2 diabetes play a negative role in the progression of liver fibrotic processes [20]. In one of the studies, it was shown that HIV-1 gp120 stimulates HCV replication and TGF-β1 expression, and the latter one is also capable of independently enhancing HCV replication [21]. Increased activity of the inflammatory process leads to the stroma infiltration by lymphocyte and macrophage cells, which secrete pro-inflammatory factors, which plays a key role in the fibrosis progression. This is indicated by the results of the study performed by Akil A. et al. (2018), who determined that HIV-infected macrophages accelerate hepatic fibrosis during HCV/HIV co-infection by amplifying the expression of HCV-dependent fibrogenic genes in hepatic stellate cells. [22].

In patients with hepatitis B+C, according to our data, there are cytopathic effects inherent to both types of viruses due to their combined effect, therefore, both types of liver dystrophy are observed at the same time – hydropic (69.8 %) and fatty (30.2 %) ones. As a result, alteration of hepatocytes in the form of periportal bridging and intralobular focal necrosis occurred in 74.4 % of cases. However, the histological activity of hepatitis was the lowest in these patients (A1 – 53.5 %, and A4 – 4.7 %), which was combined with the highest frequency of liver cirrhosis (F4 – 67.4 %). The formation of liver cirrhosis was characterized not only by the growth of connective tissue in the portal tracts, but also by the formation of pseudoparticles along with the proliferation of intrahepatic biliary ducts and pronounced angiomatosis of the stroma. Such data indicate a more rapid development of cirrhosis with the combined HBV/HCV co-infection in HIV-infected patients due to the presence of both types of liver cell dystrophy (hydropic and fatty ones), and the spread of small periportal and intralobular necrosis of hepatocytes. Against the background of the already

formed cirrhosis of the liver, inflammatory phenomena are already subsiding in these patients.

On the basis of correlation analysis, we have confirmed the fact of a decrease in HAI against the background of the progression of liver fibrosis. This may be associated with a decrease in the infiltration of the stroma by the inflammatory cells and depletion of the population of Kupffer cells in liver [23, 24].

Concomitant diseases such as pneumocystic pneumonia, tuberculosis, meningitis and encephalitis of various etiology, as well as chronic intoxication with alcohol and injectable drugs could have an additional negative impact on the morphological state of the liver, however, they had the importance of secondary factors that strengthened the primary etiological cause, which were hepatitis viruses and did not significantly change the nature of histological changes in the liver. These factors were evenly distributed between the groups, represented with the same frequency, so they made it possible to single out the changes caused by hepatotropic viruses. A statistically significant difference in histopathological changes between groups of patients, which were divided according to the type of hepatitis viruses, namely, B, C or B+C, confirmed the leading character of the viral cause of the detected changes.

## Conclusions

In HIV-infected deceased persons with hepatitis B the hydropic dystrophy of hepatocytes (87.5 %) and intralobular focal and periportal bridging necrosis of hepatocytes (100.0 %) were the most common. The fatty dystrophy of the liver was typical for patients with hepatitis C (91.7 %) against the background of weakly expressed necrotic changes in hepatocytes (12.5 %). B+C hepatitis was characterized by complex pathomorphological liver changes: the hydropic dystrophy (69.8 %), fatty dystrophy (30.2 %), necrosis of hepatocytes (74.4 %) and liver cirrhosis C (67.4 %). The increase in the degree of liver fibrosis negatively correlated with histology activity index of hepatitis, regardless of viral etiology ($r = -0.607$, $p<0.001$).

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## ПАТОМОРФОЛОГІЧНІ ЗМІНИ ПЕЧІНКИ, СПРИЧИНЕНІ ВІРУСАМИ ГЕПАТИТІВ В, С, В+С, У ПОМЕРЛИХ ВІЛ-ІНФІКОВАНИХ ХВОРИХ

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*РЕЗЮМЕ. Досліджено патогістологічні особливості препаратів печінки 75 ВІЛ-інфікованих померлих із хронічними вірусними гепатитами, у яких протягом життя діагностовано: гепатит В – у 8, С – у 24, В+С – у 43 хворих. Встановлено, що в усіх хворих (100,0 %) при будь-якому типі хронічного гепатиту (В, С або В+С) спостерігалася лімфоцитарно-макрофагальна інфільтрація портальних трактів і строми. У хворих на гепатит В вогнищевий та перипортальний некроз гепатоцитів спостерігався у 100,0 % хворих, гідропічна дистрофія гепатоцитів – у 87,5 % та цироз печінки – у 25,0 %. У хворих на гепатит С жирову дистрофію печінки виявлено у 91,7 %, причому частіше, ніж у хворих на гепатит В (12,5 %, p<0,001), менше вогнищевий перипортальний некроз гепатоцитів (12,5 % проти 100,0 %). відповідно, p<0,001) і цироз печінки був у 41,7 %.*

*У хворих на гепатит В+С були присутні ознаки, характерні як для гепатиту В, так і для С: гідропічна дистрофія (69,8 %), жирова дистрофія (30,2 %), перипортальний мостовидний некроз (51,2 %), фіброз печінки (34,9 %). Внаслідок цих комплексних патологічних процесів у печінці частіше, ніж в інших групах хворих, виявляли цироз (67,4 % проти 41,7 % хворих на гепатит С, p=0,041, та проти 25,0 % хворих на гепатит). В, p=0,024). Індекс гістологічної активності гепатиту та стадії фіброзу печінки за Knodell R.G. (1981) не відрізнялися за частотою у всіх групах хворих. У всіх пацієнтів між ними виявлено сильну негативну кореляцію (r=-0,607, p<0,001). Цей факт свідчить про зниження гістологічної активності гепатиту на фоні посилення фіброзних змін в організмі.*

***Висновок.** Встановлено, що для гепатиту В у ВІЛ-інфікованих померлих характерними є гідропічна дистрофія та вогнищевий інтралобулярний і перипортальний мостиковий некроз гепатоцитів. Гепатит С характеризується жировою дистрофією та цирозом печінки. Наявність гепатиту В+С викликає зміни печінки, характерні як для гепатиту В, так і для гепатиту С одночасно: гідропічну дистрофію, жирову дистрофію, некроз гепатоцитів. Цироз печінки найчастіше зустрічається у хворих на гепатит В+С. Ступінь фіброзу печінки негатив-*

*но корелює з індексом гістологічної активності гепатиту.*

***Ключові слова:*** *імунодефіцит, вірусна інфекція, гепатит, фіброз печінки, цироз печінки.*

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