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ТИББИЁТДА ЯНГИ КУН
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DRUG LIVER DAMAGE AS THE MAIN FACTOR OF POST-COVID 19 COMPLICATIONS

(Literature review)

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✓ ***Resume***

The pandemic of coronavirus infection COVID-19, although today it has almost become endemic, is fraught with many long-term side effects, such as liver damage. But the question arises whether it is true that it is the coronavirus infection that is the main cause of damage to this organ or many hepatotoxic substances lead to complications. In this article, we will analyze many studies conducted in different countries of the world. There are cytotoxic lesions leading to the development of acute or chronic hepatitis, cholestatic lesions associated with structural changes in the elements of the biliary system or the mechanisms of bile formation. Morphological features of lipid metabolism disorders in hepatocytes with the development of hepatic steatosis and steatohepatitis are also described. In some cases, under the influence of drugs, damage to the intrahepatic vasculature, accumulation of pigments, development of granulomatous reactions and liver fibrosis are observed.

Key words: biliary excretion process, occurrence of jaundice without signs of an obstructive component, drug-induced liver injury, factors of post-COVID complications in COVID-19

ЛЕКАРСТВЕННОЕ ПОВРЕЖДЕНИЕ ПЕЧЕНИ КАК ОСНОВНОЙ ФАКТОР ПОСТКОВИДНЫХ ОСЛОЖНЕНИЙ COVID-19

(Литературный обзор)

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✓ ***Резюме***

Пандемия коронавирусной инфекции COVID-19, хотя на сегодняшний день она практически приобрела эндемический характер, чревата многими отдаленными побочными эффектами, например поражением печени. Но возникает вопрос, правда ли, что именно коронавирусная инфекция является основной причиной поражения этого органа или многие гепатотоксические вещества приводят к осложнениям. В этой статье мы проанализируем множество исследований, проведенных в разных странах мира. Различают цитотоксические поражения, приводящие к развитию острого или хронического гепатита, холестатические поражения, связанные со структурными изменениями элементов билиарной системы или механизмов желчеобразования. Описаны также морфологические особенности нарушений липидного обмена в гепатоцитах с развитием стеатоза печени и стеатогепатита. В ряде случаев под влиянием препаратов наблюдают поражение внутрипеченочной сосудистой сети, накопление пигментов, развитие гранулематозных реакций и фиброза печени.

Ключевые слова: процесс желчевыделения, возникновение желтухи без признаков обструктивного компонента, лекарственное поражение печени, факторы постковидных осложнений при COVID-19.

GIYOHVAND MODDALAR JIGARINING ZARARLANISHI COVID 19 DAN KEYINGI ASORATLARNING ASOSIY OMILI SIFATIDA

(Adabiyotlar sharhi)

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✓ ***Rezyume***

COVID-19 koronavirus infeksiyasi pandemiyasi, garchi bugungi kunda u deyarli endemik bo'lib qolgan bo'lsa-da, jigar shikastlanishi kabi ko'plab uzoq muddatli nojo'ya ta'sirlar bilan to'la. Ammo bu organning shikastlanishiga aynan koronavirus infeksiyasi sabab bo‘layotgani rostmi yoki ko‘plab gepatotoksik moddalar asoratlarga olib keladimi, degan savol tug‘iladi. Ushbu maqolada biz dunyoning turli mamlakatlarida o'tkazilgan ko'plab tadqiqotlarni tahlil qilamiz. O'tkir yoki surunkali gepatitning rivojlanishiga olib keladigan sitotoksik lezyonlar, safro tizimining elementlari yoki safro hosil bo'lish mexanizmlaridagi tarkibiy o'zgarishlar bilan bog'liq xolestatik lezyonlar mavjud. Gepatotsitlardagi lipidlar almashinuvi buzilishining morfologik xususiyatlari, shuningdek, jigar steatozi va steatogepatit rivojlanishi bilan tavsiflanadi. Ba'zi hollarda dorilar ta'sirida intrahepatik tomirlarning shikastlanishi, pigmentlarning to'planishi, granulomatoz reaktsiyalarning rivojlanishi va jigar fibrozi kuzatiladi.

Kalit so'zlar: safro chiqarish jarayoni, obstruktiv komponent belgilarisiz sariqlikning paydo bo'lishi, dori vositasida jigar shikastlanishi, COVID-19da post-COVID asoratlari omillari

Relevance

Liver damage can be caused not only by viruses or hepatotropic toxins, but also by many drugs. As a rule, this occurs in individuals with hypersensitivity to these drugs, and is due to the individual genetic characteristics of a person. Acute damage can occur in the parenchyma of an organ due to a cytotoxic or cytolytic effect on hepatocytes, in the elements of the biliary system (cholestatic lesions) or is of a combined nature. According to various data, no more than 5% of cases of clinically detected jaundice are associated with taking medications. However, when examining patients with chronic hepatitis of unclear etiology, in 10% of cases, changes in laboratory parameters can be associated with autoimmune diseases. At the age of over 50 years, this figure is 40%. As a rule, the diagnosis of drug-induced liver injury is established by clinical and anamnestic data. Life-time morphological examination of the liver in such patients is rarely performed, therefore, data on the structural features of the liver tissue in drug-induced lesions are not systematized and scattered.

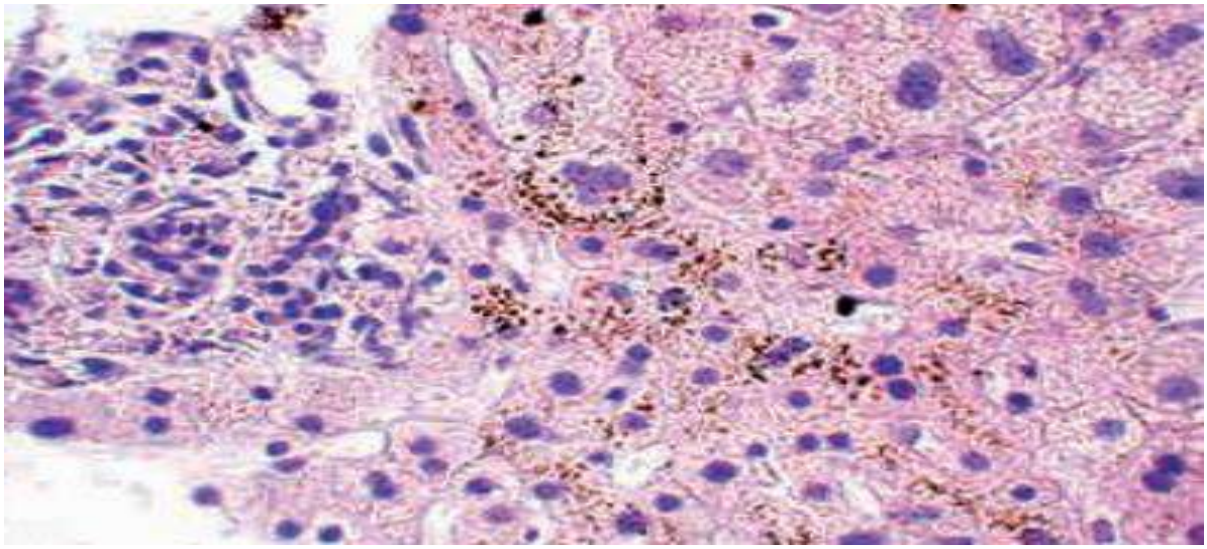
According to the materials of the Central Research Institute of Gastroenterology, when analyzing the data of a histological study of more than 1,500 puncture liver biopsies, drug-induced hepatitis was morphologically verified only in 1% of patients with clinical manifestations of chronic hepatitis. The damaging effect of toxic metabolites most often affects hepatocytes or bile duct epithelial cells.Although the pathological process may also involve vascular endothelial cells, sinusoidal macrophages (Kupffer cells), stellate cells, as well as structures of the intercellular substance. Usually, with drug-induced lesions, all structural components of the liver tissue are affected to one degree or another [2].

Morphological manifestations of hepatotoxicity of drugs cytotoxic lesions

In almost 90% of cases, drug-induced hepatitis has an acute onset. In the blood, the activity of alanine aminotransferase (ALT) more than doubles, which is a marker of hepatocyte cytolysis. An increase in alkaline phosphatase (AP) is an enzymatic marker of cholestasis, since this enzyme is present both on the apical membrane of hepatocytes and bile duct epithelial cells. The ratio of these enzymes can be used to judge the nature of the pathological process. The ALT/APL ratio ≥ 5 indicates the predominance of cytolysis, ALT/APL ≤ 2 indicates the predominance of cholestasis, and ALT/APL values from 2 to 5 indicate combined liver damage. Acute drug-induced hepatitis resembles acute viral hepatitis in many ways. Clinical manifestations are largely determined by the morphological substrate and depend on the topography and volume of necrotic liver tissue. The course varies from mild, with rapid regression in case of discontinuation of the drug, to severe, fulminant, with the development of liver failure.

Histologically, among the cells of the infiltrate of the portal tracts, plasma cells and eosinophils are often found, and the violation of the integrity of the border plate with the development of periportal hepatitis and fibrosis is typical of an autoimmune lesion. Less severe morphological manifestations of liver damage, accompanied by the appearance of antibodies to smooth muscle actin, can be caused by drugs such as ticrinafen, iproniazid, and halothane [1,7]. On the other hand, drugs such as sulfonamides, uracil, can lead to the appearance of morphological signs of autoimmune hepatitis, but are not accompanied by the production of autoantibodies [6,8]. Other morphological manifestations of chronic drug-induced liver injury, caused, for example, by long-term use of methotrexate, include hepatocyte steatosis, balloon dystrophy, anisokaryosis with hyperchromia or vacuolization of the nuclei in combination with excessive development of connective tissue. The rapid progression of fibrosis with subsequent formation of cirrhosis may be due to the intake of arsenic compounds or vinyl chloride, as well as in cases of hypervitaminosis A [4,9]. Hepatitis of medicinal etiology should first of all be differentiated from viral hepatitis and autoimmune lesions. Serological data for the presence of hepatotropic viruses (B, C, D, E, G, TT, etc.) or the presence of autoantibodies are of paramount importance in differential diagnosis. On histological examination, lymphocytic infiltration of the portal tracts is more pronounced in hepatitis of viral etiology, while the presence of eosinophils or macrophages suggests a medical lesion. See picture 1.

Figure 1. Morphological picture of drug-induced liver injury in a patient with coronavirus infection.



Parenchymal tubular cholestasis. Bile granules are visible not only in the bile ducts, but also in the cytoplasm of hepatocytes of the periportal zone. Stained with hematoxylin and eosin. Increased ×500

It should also be taken into account that the presence of autoantibodies may be due to the induction of the body's immune system by certain drug metabolites.

Medicines can cause small droplet or large droplet obesity of hepatocytes. A more severe form is the development of small droplet obesity, when many small lipid inclusions fill the cytoplasm of the hepatocyte without leading to a peripheral displacement of its nucleus. The severity of damage is due to the blockade of chains of oxidative metabolism in mitochondria. Violation of oxidative phosphorylation leads to the formation of defective enzymes, damage to mitochondrial DNA, a sharp change in the structure of mitochondria, followed by necrosis of hepatocytes [5]. This condition has similar features with some hereditary diseases caused by a defect in mitochondrial enzymes [10]. Drugs that can cause hepatic steatosis include aspirin (acetylsalicylic acid), paracetamol, hydroxychloroquine, dexamethasone, which are often used in the treatment of COVID-19.

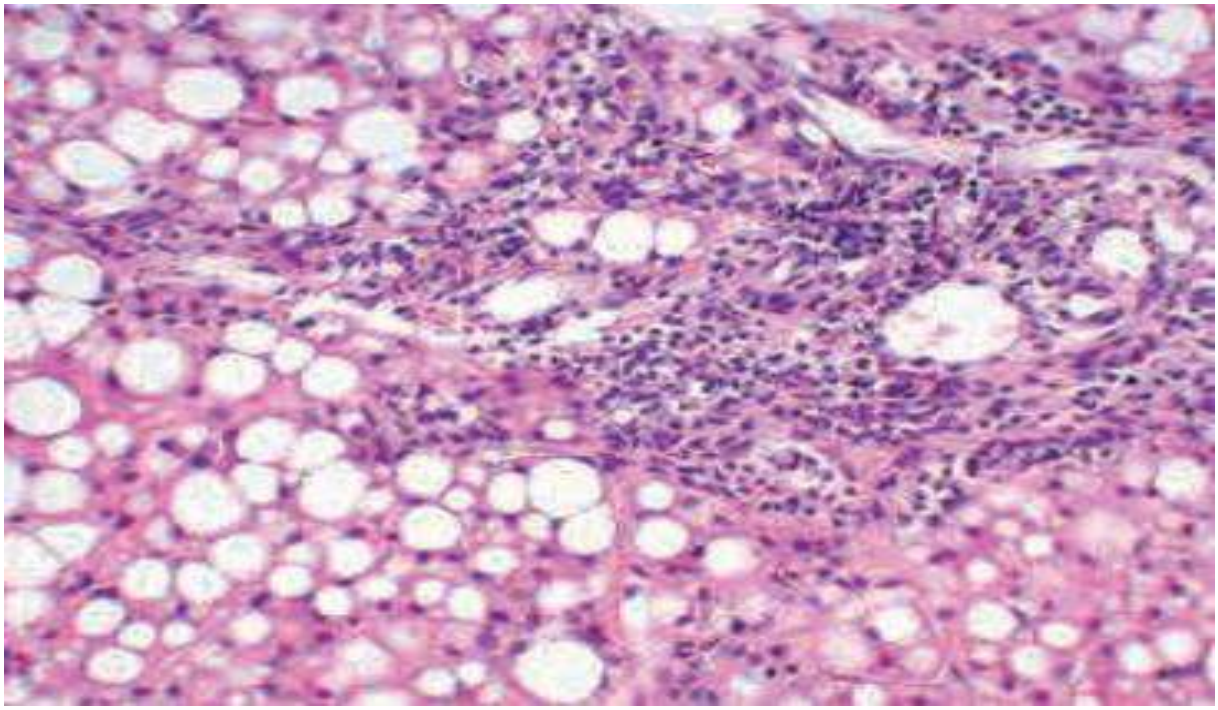
Granulomatous reactions may be the only manifestation of drug-induced liver injury or may accompany other, more severe manifestations such as cytolysis or cholestasis. The mediators in the pathogenetic mechanisms of the development of the granulomatous reaction are activated Kupffer cells, macrophages and neutrophils that produce various cytokines and cytotoxic substances. Depending on the nature of the toxic factor and the individual sensitivity of the organism, these substances can play

both a protective role and have a pathogenic effect [11]. Most drugs cause the formation of non-caseating epithelioid granulomas of various sizes, located in the portal tracts or inside the hepatic lobules.

Fibrosis develops in most drug-induced liver lesions, but only in a few is it the predominant feature. Substances associated with this type of drug-induced liver injury are cytostatics (methotrexate), vitamin A and other retinoids, and arsenic compounds. Damage is due to the action of toxic drug metabolites and is usually localized in the pericentral zone, although periportal fibrosis may develop with methotrexate. Fibrous tissue is formed from bundles of collagen fibers, localized compactly in the spaces of Disse. This impairs blood flow in the sinusoids, causing non-cirrhotic portal hypertension and hepatocyte dysfunction. The clinical manifestation of this type of drug-induced liver injury is non-cirrhotic portal hypertension. In the pathogenetic mechanisms of the development of liver fibrosis, the leading role belongs to stellate cells.

Liver stellate cells are located between the endothelial cells lining the sinusoidal spaces and hepatocytes. Their cytoplasm is filled with lipid inclusions, clearly visible in a light microscope. Hypertrophy of stellate cells is observed with the expansion of the sinusoids and the development of perisinusoidal fibrosis. With hypervitaminosis A, the number and size of lipid inclusions in stellate cells increases (Fig. 2, see).

Figure 2. Morphological picture of drug-induced liver injury in a patient with coronavirus infection.



Steatohepatitis at the stage of liver cirrhosis formation: a) severe inflammatory infiltration of portal tracts, destruction of ductules, multiple connective tissue septa. Stained with hematoxylin and eosin. Increased ×500; b) the formation of false lobules. Coloring according to van Gieson. Increased ×120

This condition usually remains asymptomatic for a long time, but gradually leads to the development of perisinusoidal fibrosis and even cirrhosis of the liver with portal hypertension [4]. The development of perisinusoidal fibrosis is a consequence of the activation of stellate cells - their myofibroblastic transformation. The marker of this process is the expression of smooth muscle α-actin in their cytoplasm, while expression of retinol-binding protein-1 is characteristic of non-activated stellate cells [12]. Some hepatotoxic drugs, such as methotrexate, immunosuppressants, also lead to the activation of stellate cells, which is not accompanied by an increased accumulation of lipids in their cytoplasm, but also ends with the formation of perisinusoidal fibrosis.

Treatment and prognosis. In most cases, drug-induced liver injury does not require special treatment. The main requirement is to stop taking the drug that caused this lesion. The use of corticosteroids to relieve immunoallergic manifestations does not always bring the desired result. Ursodeoxycholic acid preparations are prescribed as symptomatic therapy to relieve itching and compensate for metabolite malabsorption in

cholestatic lesions [9]. In forms with a predominance of cytotoxic lesions (chronic hepatitis, steatohepatitis), it is advisable to use hepatoprotectors. Hepatoprotectors are a group of drugs of natural and synthetic origin that increase the resistance of the liver to the action of pathogenic factors, accelerate the processes of its regeneration and normalize functional activity. Hepatoprotectors of plant origin include preparations based on milk thistle (for example, legalon). They contain a complex of flavonoids, which provide an antioxidant and antifibrotic effect and activate the synthesis of albumins. Hepatoprotectors of animal origin contain essential phospholipids that contribute to the activation and protection of phospholipid-dependent enzyme systems. They improve the detoxification function of the liver, restore its cellular structure, improve regeneration and inhibit the formation of connective tissue in it.

Conclusion

In cases where it is possible to recognize the drug that caused drug damage in time and stop taking it before the onset of severe organic changes in the liver, the prognosis of the disease is favorable. The occurrence of jaundice without signs of an obstructive component while taking a hepatotoxic drug increases the risk of an unfavorable outcome, as it indicates the inability of hepatocytes to provide the process of bile excretion.

LIST OF REFERENCES:

1. Abdullaeva M.A., Inoyatov. A.SH. Eksperimental va klinik onkologiyada ionlashtiruvchi nurlanish. // *O`zbekiston vrachlar associaciyasining byulleteni* 2022; 2:33-36.
2. Drapkina O.M., Maev I.V., Bakulin I.G. i dr. Vremennye metodicheskie rekomendacii: «Bolezni organov pishchevareniya v usloviyah pandemii novoj koronavirusnoj infekcii (COVID-19)» [Interim guidelines: «Diseases of the digestive system in the context of the novel coronavirus infection (COVID-19) pandemic»] // Profilakticheskaya medicina [The Russian Journal of Preventive Medicine]. 2020; 23(3):2120–2152. Doi:10.17116/profmed202023032120. (In Russ.; abstr. in Engl.).
3. Ivashkin V.T., Sheptulin A.A., Zol'nikova O.Yu. i dr. Novaya koronavirusnaya infekciya (COVID-19) i sistema organov pishchevareniya [New Coronavirus Infection (COVID-19) and Digestive System] // *Rossijskij zhurnal gastroenterologii, gepatologii, koloproktologii* [*Russian Journal of Gastroenterology, Hepatology, Coloproctology*]. 2020; 30(3):7-13. URL: https://doi.org/10.22416/1382-4376-2020-30-3-7. (In Russ.; abstr. in Engl.).
4. Zaripova D.Ya., Tuksanova D.I., Negmatullaeva M.N. Osobennosti techeniya perimenopauzal'nogo perekhoda zhenshchin s ozhireniem. // *Novosti dermatovenerologii i reproduktivnogo zdorov'ya*. 2020; 1-2:39-42.
5. Abdullaeva M.A., Kosimova D.S. Evalution of the quality of life of patients with cirrhosis after surgical prevention of bleeding from varicoseveins of the esophagus // *Hindustan International journal for innovative engineering and management research* 2020; 9(11):185-189.
6. Bioquard L., Valla D., Rautou P.-E. No evidence for an increased liver uptake of SARS-CoV-2 in metabolic associated fatty liver disease // *J. Hepatol*. 2020; 73(3):717-718. doi: 10.1016/j.jhep.2020.04.035.
7. Chen N., Zhou M., Dong X., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study // *Lancet.* 2020; 395:507–513. doi: 10.1016/S0140-6736(20)30211-7.
8. Cholankeril G., Podboy A., Aivaliotis V.I., et al. High prevalence of concurrent gastrointestinal manifestations in patients with SARS-CoV-2: Early Experience from Californi // *Gastroenterology.* 2020; 159(2):775–777. doi: 10.1053/j.gastro.2020.04.008.
9. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists // *BMJ*. 2020; 368:1086. doi: 10.1136/bmj.m1086.
10. Falcao M.B., de Goes Cavalcanti L.P., Filho N.M. F., Antunes de Brito C.A. Case report: hepatotoxicity associated with the use of hydroxychloroquine in a patient with novel coronavirus disease (COVID-19) // *Am. J. Trop. Med. Hyg*. 2020; 102(6):1214-1216. doi: 10.4269/ajtmh.20-0276.
11. Feng G, Zheng K.I., Yan Q.Q., Rios R.S., et al. COVID-19 and liver dysfunction: current insights and emergent therapeutic strategies // *J Clin Transl Hepatol*. 2020; 8(1):18-24. doi: 10.14218/JCTH.2020.00018.
12. Zaripova D.Ya., Nigmatullaeva M.N., Toksanova D.I., Ashurova N.G. The effect of magnesium deficiency and imbalance of steroid hormones in the life of the woman //New Day in Medicine 2019; 3(27):14-17 https://newdaymedicine.com/index.php/2019/10/10/3-3-27-1-2019

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