DOI: https://doi.org/10.17816/EID627312

Фиброзирующий холестатический гепатит как вариант течения инфекции, вызванной гепатотропными вирусами

В.Е. Сюткин[1], В.П. Чуланов[2]

[1] Научно-исследовательский институт скорой помощи имени Н.В. Склифосовского, Москва, Россия;
[2] Национальный медицинский исследовательский центр фтизиопульмонологии и инфекционных заболеваний, Москва, Россия

АННОТАЦИЯ

Фиброзирующий холестатический гепатит — особый вариант течения инфекционного гепатита, характеризующийся быстрым прогрессирующим ухудшением функции печени; обычно развивается в условиях иммуносупрессии, хотя описан и у иммунокомпетентных больных вирусными гепатитами В и С. В основе диагностики фиброзирующего холестатического гепатита лежит гистологическое исследование ткани печени, при котором выявляют преобладание повреждения гепатоцитов с их выраженной баллонной дистрофией над слабой воспалительной реакцией, перицеллюлярный и перисинусоидальный фиброз, а также внутриклеточный и канальцевый холестаз. Анализ литературы подтверждает предположение авторов о том, что патологические изменения в печени, описанные как фиброзирующий холестатический гепатит, могут развиваться в различных условиях под воздействием различных инфекционных агентов. Несмотря на наличие эффективной противовирусной терапии гепатитов В и С, исходы фиброзирующего холестатического гепатита часто неблагоприятны, особенно в случаях, не связанных с трансплантацией солидных органов. В настоящее время в связи с появлением большого количества лекарств, избирательно действующих на иммунную систему, развитием новых направлений медицины в гематологии, ревматологии, онкологии, трансплантологии, инфекционных болезнях, врачи этих специальностей все чаще сталкиваются с неожиданно тяжёлыми формами поражения печени на фоне проводимой специфической терапии. Авторы полагают, что имеет место недооценка врачами, не работающими в Центрах трансплантации печени, возможности развития фиброзирующего холестатического гепатита у больных с вирусными гепатитами В и С в клинике как инфекционных, так и внутренних болезней.

Ключевые слова: инфекционный гепатит; фиброзирующий холестатический гепатит; HBV; HCV; трансплантация органов; серонегативный гепатит.

Как цитировать:
Сюткин В.Е., Чуланов В.П. Фиброзирующий холестатический гепатит как вариант течения инфекции, вызванной гепатотропными вирусами // Эпидемиология и инфекционные болезни. 2024. Т. 29, № 2. С. 126–141. DOI: https://doi.org/10.17816/EID627312

Рукопись получена: 21.02.2024 **Рукопись одобрена:** 07.03.2024 **Опубликована online:** 09.04.2024

DOI: https://doi.org/10.17816/EID627312

Fibrosing cholestatic hepatitis as a variant of the course of hepatotropic viruses' infection

Vladimir E. Syutkin[1], Vladimir P. Chulanov[2]

[1] N.V. Sklifosovsky Research Institute of Emergency Medical Care, Moscow, Russia;
[2] National Medical Research Center for Phthisiopulmonology and Infectious Diseases, Moscow, Russia

ABSTRACT

Fibrosing cholestatic hepatitis is a special variant of infectious hepatitis, with a rapid progressive deterioration of liver function, and usually results in immunosuppression. It has also been reported in patients with immunocompetent status having viral hepatitis B and C. Fibrosing cholestatic hepatitis is diagnosed based on the histological examination of the liver tissue, which reveals severe damage to hepatocytes with pronounced ballooning over a weak inflammatory reaction, pericellular and perisinusoidal fibrosis, and intracellular and tubular cholestases. Analysis of the literature confirms the authors' assumption that pathological changes in the liver, described as fibrosing cholestatic hepatitis, can develop in different conditions under the influence of various infectious agents. Despite the availability of effective antiviral therapy for hepatitis B and C, the outcomes of fibrosing cholestatic hepatitis are often unfavorable, particularly in cases not associated with solid-organ transplantation. Currently, because of the emergence of numerous drugs that selectively act on the immune system and the development of new areas of medicine such as hematology, rheumatology, oncology, transplantology, and infectious diseases, doctors in these specialties increasingly encounter severe liver damage in patients receiving specific therapy. The authors believe that doctors who do not work at liver transplantation centers underestimate the possibility of fibrosing cholestatic hepatitis development in patients with viral hepatitis B and C, in the clinic of infectious and internal diseases.

Keywords: infectious hepatitis; fibrosing cholestatic hepatitis; HBV; HCV; organ transplantation; seronegative hepatitis.

To cite this article:
Syutkin VE, Chulanov VP. Fibrosing cholestatic hepatitis as a variant of the course of hepatotropic viruses' infection. *Epidemiology and Infectious Diseases.* 2024;29(2):126–141. DOI: https://doi.org/10.17816/EID627312

Received: 21.02.2024 **Accepted:** 07.03.2024 **Published online:** 09.04.2024

INTRODUCTION

In recent decades, new variants of the course of infectious hepatitis that go beyond the classic acute and chronic hepatitis have been described, particularly for hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. For HBV infection, the classical concepts of the immunotolerant phase have been revised [1, 2]. Reactivation of HBsAg-negative hepatitis in anti-HBcor carriers undergoing immunosuppressive therapy represents a distinct variant of the course. A common occurrence is de novo hepatitis B developing in liver transplant recipients [3]. This phenomenon has led to the formulation of the concept of acute hepatitis versus chronic hepatitis. Additionally, the possibility of a chronic course of hepatitis E virus (HEV) infection in the context of immunosuppression (IS) has been demonstrated [4].

Fibrosing cholestatic hepatitis (FCH) is a distinctive form of the infectious hepatitis course, characterized by a progressive deterioration of liver function from several weeks to months. This variant of the course typically develops in individuals with IS, although it has been documented in immunocompetent patients with viral hepatitis B and C.

ETIOLOGY AND EPIDEMIOLOGY

The pattern of liver damage, designated FCH, was initially described in the early 1990s in liver transplant (LT) recipients with recurrent HBV infection [5, 6]. Notably, the initial report on the development of FCH as a distinct course of HCV infection following LT was conducted by Schluger et al. [7]. Nevertheless, in 1994, a team of physicians from the University of Florida (USA) presented a case of severe cholestatic liver damage with a histologic picture characteristic of FCH in a recipient who had received an HCV-infected heart transplant [8]. Most cases of FCH have been described in LT recipients. However, since the early 1990s, there have been reports of the development of this pattern of liver damage in recipients of transplantation of other solid organs and bone marrow and, later, outside the context of organ transplantation. Cases of FCH caused by hepatitis B or C viruses have been described in patients with autoimmune, oncologic, and hematologic diseases during specific therapy, those infected with human immunodeficiency virus (HIV), and immunocompetent individuals. Table 1 presents a summary of these reports. Several studies from Southeast Asia have reported the development of FCH in cytomegalovirus (CMV) infection. These reports have been published in the context of both recipients of a transplanted organ [9, 10] and immunocompetent patients [11]. Additionally, Spanish authors have confirmed the possibility of FCH development after kidney transplantation in CMV infection [12]. Recently, researchers from India have discussed the potential role of parvovirus B19 in FCH development in kidney transplant recipients [13]. Furthermore, a report from Germany did not entirely rule out the possible role of adenovirus infection in the FCH development after kidney transplantation. However, those authors exercised considerable caution in their conclusions, indicating that superinfection with adenovirus may have resulted in extensive liver necrosis in a patient with FCH caused by HBV infection [14].

Prior to the widespread implementation of immunoprophylaxis for recurrent HBV infection in LT recipients, FCH posed a significant challenge for LT recipients,

Table 1. Case reports of fibrosing cholestatic hepatitis in patients with HBV or HCV infection, excluding those in liver transplantation

Conditions	HBV	HCV
Immunocompetent individuals	Sutherland et al. (2019) [19]; Philips et al. (2019) [20]	Akagi et al. (2014) [21]
Hemodialysis	Wong et al. (2006) [22]	–
HIV	Fang et al. (1993) [23]; Poulet et al. (1996) [24]	Rosenberg et al. (2002) [25]; Moreno et al. (2006) [26]
Autoimmune, hematologic, and oncologic diseases	Lee et al. (2000) [27]; Kojima et al. (2002) [28]; Jung et al. (2002) [29]; Wasmuth et al. (2008) [30]; Zanati et al. (2004) [31]; Ceballos-Viro et al. (2009) [32]; Topaloglu et al. (2014) [33]	Nassar et al. (2018) [34]; Morii et al. (2012) [35]; Saleh et al. (2007) [36]; Pellicelli et al. (2015) [37]
Kidney transplantation	Chen et al. (1994) [38]; Hung et al. (1995) [39]; Booth et al. (1995) [40]; Al Faraidy et al. (1997) [41]; Lam (1996) [42]; Brind et al. (1998) [43]; Waguri et al. (1998) [44]; Toth et al. (1998) [45]; Muñoz de Bustillo et al. (2001) [12]; Chan et al. (1998) [46]; Lee et al. (2000) [27]; Jung et al. (2002) [29]	Zylberberg et al. (1997) [47]; Muñoz de Bustillo et al. (1998) [48]; Delladetsima et al. (1999) [49]; Delladetsima et al. (2006) [50]; Boletis et al. (2000) [51]; Hooda et al. (2006) [52]; Shores et al. (2008) [53]; Honsová et al. (2011) [54]; Siddiqui et al. (2012) [55]; Li et al. (2015) [56]; Shinzato et al. (2019) [57]; Kapila et al. (2020) [58]
Heart transplantation	–	Lim et al. (1994) [8]; Delgado et al. (1999) [59]; Ong et al. (1999) [60]; Liu et al. (2017) [61]
Hematopoietic cell transplantation	McIvor et al. (1994) [62]; Suresh et al. (2001) [63]	Evans et al. (2015) [64]

accounting for 33%–42% of recurrent hepatitis B (or HBV/HDV coinfection) [15]. Since the 2000s, FCH B has been increasingly described in unexpected conditions, typically unrelated to transplantation (Table 1). A comparable phenomenon was observed in liver recipients undergoing surgical procedures for terminal-stage chronic hepatitis C prior to the advent of direct-acting antivirals (DAAs) in routine clinical practice. Up to 10% of patients with relapsing hepatitis C acquired FCH [16]; treatment of these patients with pegylated interferon preparations was rarely observed [17]. FCH risk increased if the recipients were also infected with HIV, which negatively affected the survival of grafts and recipients. For example, FCH was the cause of 38% of deaths in liver recipients with HCV/HIV coinfection [18].

HISTOLOGIC CHANGES AND DIAGNOSTIC CRITERIA

The histologic changes observed in FCH represent a unique pattern of liver damage that is qualitatively distinct from that observed in typical acute and chronic hepatitis variants. These changes are characterized by the predominance of hepatocyte damage with pronounced balloon dystrophy, in the absence of a robust inflammatory response. Minimal infiltrate in portal tracts and lobules with rapid development of pericellular (perisinusoidal) fibrosis, and intracellular and tubular cholestasis are reflected in the name of the syndrome, which has not changed since its first description.

The development of diagnostic criteria for FCH was initiated by the expert community, coinciding with the decline in the prevalence of FCH B in the clinical practice of transplantologists due to the introduction of effective combined prophylaxis against HBV infection reactivation. The diagnostic criteria for FCH C were initially proposed in 2003 at a conference on HCV infection following LT. Consequently, FCH C was defined as a disease occurring not earlier than the second month after LT, with a serum bilirubin content >6 mg/dL, and alkaline phosphatase and gamma-glutamyl transpeptidase activities five or more times higher than the normal upper limits. In addition to the aforementioned histologic features, the presence of balloon dystrophy of hepatocytes in the perivenular zone, mild inflammation, and varying degrees of cholangiolar proliferation without loss of bile ducts is crucial. Furthermore, the blood HCV RNA content should be extremely high and the absence of biliary complications or hepatic artery thrombosis evident [65].

Some authors from the Mayo Clinic (Rochester, USA) proposed to refine the set of diagnostic criteria (Table 2) [66] based on their own well-founded studies. All criteria are divided into three groups: specific, auxiliary, and exclusion criteria. The diagnosis of FCH is based on the histologic features of the disease, which were clearly described. Auxiliary criteria included a total bilirubin ⩾2 mg/dL. The value was found to be significantly lower than the threshold value of 6 mg/dL proposed by the 2003 consensus conference. This was because a bilirubin level <2 mg/dL had a 100% negative predictive value, which allowed for the exclusion of FCH C. Interestingly, the authors considered older age of the donor and recent rejection as auxiliary criteria, whereas the level of HCV viremia did not play a decisive role in the diagnosis of FCH C. These criteria were confirmed by the authors in comparison with patients with recurrent hepatitis C with minimal and severe fibrosis. The same group of authors proposed a similar approach to assess the severity of recurrent hepatitis C after LT, assuming that "conventional hepatitis" can progress into FCH under certain conditions [67].

Table 2. Diagnostic criteria for cholestatic hepatitis C [66]

Criteria	Description of features
I. Specific criteria	Histologic criteria (at least 3 of the following 4): 1. A marked ductal reaction resembling biliary obstruction in most portal tracts 2. Cholestasis (defined as tubule bile plugs and/or intracellular bile pigment) 3. Expressed balloon dystrophy of hepatocytes with disruption of lobule structure 4. Any degree of periportal sinusoidal/pericellular fibrosis Timing: >1 month post-transplant
II. Supporting criteria	Blood bilirubin ⩾2 mg/dL Gamma-glutamyl transpeptidase activity ⩾150 IU/L Asparagine aminotransferase activity ⩾70 IU/L Older age of the donor Recent biopsy-confirmed acute rejection (Banff rejection activity index ⩾5)
III. Exclusion criteria	Biliary obstruction Hepatic artery thrombosis

Despite the scientific approach taken by researchers to develop diagnostic criteria and their subsequent validation, some experts have criticized these criteria as "not sufficiently clarifying the nature" of FCH [68]. Moreover, whether these criteria can be extrapolated to FCH of other (non-HCV) etiologies and FCH C outside the context of LT remains unclear. Furthermore, it should be considered that FCH may develop earlier in LT recipients [69, 70]. Conversely, Siddiqui et al. reported four cases of FCH manifesting in kidney recipients between 1.5 and 10 years after transplantation. The patients did not have HCV infection markers (both anti-HCV and HCV RNA) in their blood before transplantation and apparently acquired HCV infection post-transplant [55]. We believe that both sets of diagnostic criteria may be employed to diagnose HCV infection following LT, with an adjustment for the order of the surgery performed (primary and repeat).

SUSPECTED PATHOGENESIS

The pathogenesis of FCH remains poorly understood [15, 71, 72]. It is believed that hepatocyte damage in FCH is caused by the direct cytopathic action of the virus, with minor immune inflammation, along with high viremia and a large number of virions in hepatocytes. High HBV antigen expression (HBsAg and HBcAg) was confirmed by immunohistochemical staining (IHS) of the affected liver and evaluated by quantitative analysis (radioimmune analysis of tissue homogenates). Notably, the accumulation of HBV surface antigen in the endoplasmic reticulum and Golgi complex may result in damage to these organelles and, consequently, hepatocyte death by apoptosis or necrosis, depending on the severity of the "overload." The role of HBV mutant variants with impaired replication in HBV pathogenesis is discussed. Several HBV mutations have been reported in patients with FCH, including precore and pre-S. Moreover, it has been postulated that the latter mutation is responsible for the intracellular retention of the virus. The genome of the mutant HBV isolated from a patient with FCH resulted in high surface antigen expression when infected in cell culture. However, FCH caused by wild-type HBV has been observed, and hepatocytes with a matte-glassy cytoplasm are a common histologic finding in all variants of chronic hepatitis B.

High viremia levels and virion overload of hepatocytes have been determined in the pathogenesis of FCH C. Furthermore, it has been demonstrated that recipients with mild forms of relapsing hepatitis C exhibit higher genetic diversity of the virus population (heterogeneous quasispecies) than recipients with FCH. Conversely, the virus quasispecies becomes more homogeneous in patients with severe relapse, although this association is controversial. Individuals with FCH show a predominant Th response type 2, with more pronounced interleukin-10 and interleukin-4 activity, in contrast to patients with conventional relapsing hepatitis C who have a predominant Th response type 1 (interleukin-2, interferon-gamma). FCH C has been described in all known virus genotypes. It can be assumed that the influence of both viruses on the course of hepatitis is not the sole determining factor in the development of HBV and HCV infection.

The causes of the development of conventional hepatitis in some cases and FCH in others remain unclear. Classical ideas about this variant of the course of HBV and HCV infections assume the mandatory presence of IS; however, the nature of changes in cellular immunity in HIV and drug-induced IS after transplantation is different. In HIV, CD4+ lymphocytes are predominantly affected, whereas maintenance IS after transplantation is primarily aimed at limiting the population and activity of cytotoxic lymphocytes. A recent case report described the observation of FCH C in a patient following liver retransplantation. Despite receiving standard IS therapy, the patient developed severe bacterial infection, resulting in the cessation of supportive IS. However, FCH developed early in the absence of drug-assisted IS [70].

Researchers from the University of Texas have identified a similar liver damage pattern in yellow fever, wherein the immune status of the host is normal but the viruses are highly hepatotropic and virulent. Infection leads to rapid and severe apoptosis and necrosis of hepatocytes, often causing fulminant liver damage. The process is either rapidly fatal or ends in spontaneous recovery with liver regeneration without fibrosis [15].

FIBROSING CHOLESTATIC HEPATITIS AND HEMATOPOIETIC CELL TRANSPLANTATION

Several reports have documented the occurrence of FCH in individuals who have undergone bone marrow or hematopoietic cell transplantation. Previous studies have revealed that rapidly progressive hepatitis with an FCH pattern is more likely to result from infection with mutant precore HBV than from a wild-type variant of the virus. Thus, Angus et al. examined 10 patients infected with wild-type HBV and 10 patients with precore mutation who underwent LT and observed that all recipients exhibited recurrent HBV infection. However, only one recipient with wild-type virus exhibited graft loss, whereas seven recipients with precore mutant virus showed graft loss, with five of them exhibiting FCH. This pattern of hepatitis B infection has only been observed in patients with mutant virus [73]. Fang et al. determined that mutant precore strains are more likely to be associated with massive virus replication owing to the absence of HBe-antigen, which allows the virus to evade recognition by the immune system [74]. Notably, precore mutant strains persist after seroconversion of HBeAg to anti-HBe [75]. Moreover, McIvor et al. discussed the role of precore mutant strains in the development of fatal FCH in bone marrow recipients [62, 76]. In contrast, Suresh et al. revealed that the virus secreted HBeAg after reactivation during IS. Therapy with lamivudine was ineffective [63]. Evans et al. reported

three cases of FCH C after hematopoietic cell transplantation. In one case, acute HCV infection was noted, and in the other two cases, reactivation of chronic HCV infection was observed [64]. The observations presented by these authors were conducted at a time when interferon-free regimens for hepatitis C were unavailable. Unfortunately, all the described cases of FCH after bone marrow transplantation, regardless of etiology (HBV or HCV) and duration of infection (acute or reactivation of chronic hepatitis), ended fatally [62–64].

SERONEGATIVE FIBROSING CHOLESTATIC HEPATITIS

In some cases, HCV develops without the presence of HCV antibodies, presenting a diagnostic and prevention challenge. One of the earliest studies to report four cases of seronegative FCH C in kidney recipients was performed by Delladetsima et al. [49]. All four patients received triple supportive IS (azathioprine, cyclosporine, and methylprednisolone). The interval between kidney transplantation and the onset of liver dysfunction symptoms ranged from 1 to 4 months, whereas the interval between transplantation and the histologic diagnosis ranged from 3 to 11 months. All recipients were HCV RNA negative at the time of transplantation; however, HCV RNA was detected at the time of the first liver biopsy. In two recipients, seroconversion to anti-HCV occurred after 3 and 31 months, respectively. The other two recipients died of sepsis and liver failure 16 and 18 months after transplantation. In contrast, patients with seroconversion showed significant improvement. Subsequently, the same group of authors reported 17 cases of kidney transplantation in recipients who were seronegative at the time of transplantation but who developed hepatitis C of varying severity after surgery [50]. Furthermore, Shores and Kimberly reported a case of FCH C in a seronegative patient who underwent renal transplantation in 2004. The diagnosis was not made until 13 months after the onset of symptoms. At the time the study was published, the patient had lost both his kidney and liver and was on the waiting list for renal and hepatic transplantation [53].

Early detection of seronegative HCV infection is critical at all stages of transplantation. Prior to the advent of DAAs, an organ from an HCV-infected patient was discarded and could not be transplanted. Patients awaiting a kidney continued to receive renal replacement therapy. Following the introduction of DAAs into routine clinical practice, organ transplantation from HCV-infected donors is authorized in most countries worldwide. Prompt administration of these drugs prevents infection in the liver or contributes to the rapid cure in the initial stages of recurrent hepatitis in LT. A negative anti-HCV blood test result in the donor may result in a delayed diagnosis of HCV infection in the recipient, which in turn may progress to FCH. As previously mentioned, graft dysfunction developed already in the first month after liver retransplantation. Seronegative HCV seronegative FCH was diagnosed at the end of the second month, and HCV antibodies appeared in the blood only several months after effective antiviral therapy (AVT) [70]. The source of infection may be transfused blood components, donor organs, or the recipient himself, who may have had a latent or recently acquired infection before transplantation. The possibility of FHC C in anti-HCV seronegative patients with a pattern of rapidly progressive cholestatic liver dysfunction developed during IS is critical, not only in the context of solid-organ transplantation.

HIV COINFECTION

In 1993, the University of Florida first reported a case of severe acute liver failure in a patient with cirrhosis coinfected with HIV. The authors proposed that the presence of anti-HBc IgM antibodies indicated reactivation of HBV infection. The patient died of hemorrhagic pancreatitis. Autopsy revealed both submassive necrosis of liver parenchyma and diffuse balloon degeneration of hepatocytes with marked cholestasis and minimal inflammatory infiltrates [23]. Another publication in French is available in the PubMed database as an abstract [24]. In both cases, IHS revealed marked expression of viral antigens. It is paradoxical that HBV infection-related liver damage, which is an immune-mediated process, is exacerbated by HIV infection. Possibly, FCH, similar to severe chronic hepatitis B, does not develop as a consequence of an anti-HBV-specific immune response, but rather because of the cytotoxic action of HIV or HIV-induced mutations in HBV, which in turn enhances the cytotoxic properties of HBV. In a 2007 study, Revill et al. identified a novel mutation in the precore/core region of the HBV genome that is more prevalent in individuals coinfected with HIV and HBV than in those infected with HBV alone. Individuals coinfected with this mutation exhibited higher HBV DNA content than those without the mutation [78].

Various studies have addressed the development of FCH C in HIV-infected recipients of solid organs, primarily the liver. However, even in the absence of a transplantation context, there have been reports on the development of FCH C in HIV coinfection. For example, Rosenberg et al. reported two cases of FCH in HIV-coinfected patients who developed rapidly progressive hepatic failure, which ended fatally. HCV RNA levels were not markedly elevated in these cases, indicating that the cytopathic effect of HCV in the patients was not a consequence of an excess viral load. The authors hypothesized that rapid (within a few months) development of liver cirrhosis is part of FCH progression. They observed such development of the disease in one of their patients within 3 months [25]. Moreover, Eyster et al. conducted a study comparing HCV RNA levels before and after HIV seroconversion in patients infected with HCV and revealed that HCV RNA levels were elevated eightfold in patients with HIV coinfection compared with those with HCV mono-infection. Additionally, the number of CD4+ T cells in these patients correlated with HCV RNA levels [79].

In 2006, researchers from Spain described an unusual liver pathology in patients infected with HIV and HCV. They reported two cases of syncytial giant cell hepatitis (SGCH), one of which exhibited features of FCH during prednisone therapy. In addition to the histologic changes characteristic of chronic hepatitis C, the hepatic beams were replaced by syncytial giant cells with up to 30 nuclei. No evidence of measles or other paramyxoviruses and herpes virus infection was found. This observation was followed by the death of one patient and successful treatment of SGCH with pegylated interferon and ribavirin in the other patient [26].

NON-TRANSPLANTATION FIBROSING CHOLESTATIC HEPATITIS

Observations of FCH that developed outside the context of organ and tissue transplantation are of particular interest. One of the first such observations was published by Korean researchers in 2000, who reported a case of fatal FCH B in a 30-year-old HBsAg+ man after chemotherapy for acute lymphoblastic leukemia [27]. Subsequently, physicians from Japan reported the reactivation of HBV infection (HBsAg+/anti-HBe+) with a histologic FCH pattern after chemotherapy with cytosine arabinoside, daunorubicin, mitoxantrone, and etoposide in a patient with acute myeloblastic leukemia [28]. The patient died of fulminant hepatic failure (FHF). Additionally, researchers from Germany have reported the reactivation of HBsAg+/anti-HBe+ inactive chronic hepatitis B (previously referred to as a viral carrier) in a patient with non-Hodgkin's lymphoma following six courses of therapy with rituximab, fludarabine, and cyclophosphamide, which resulted in FCH [30]. The patient succumbed to septic shock complicated by liver failure. Another case of FCH development during treatment of non-Hodgkin's lymphoma with a rituximab-containing regimen was investigated by a study conducted in Italy. In this study, HCV reactivation in a patient with chronic hepatitis C with minimal activity and fibrosis prior to the commencement of chemotherapy was observed. This patient received effective AVT with pegylated interferon and ribavirin and died of lymphoma progression in conjunction with HCV viremia [37]. A commonality among these cases is the preexistence of inactive viral hepatitis, with subsequent reactivation of the viral infection during chemotherapy for oncohematologic disease. The histologic picture in all described observations corresponded not to massive necroses with pronounced inflammatory infiltration, but to FCH.

The initial report on the development of FCH B following standard chemotherapy for a solid tumor (small cell lung cancer) was published by researchers from Spain. Liver damage was observed in a patient without HBsAg in the blood, but with evidence of HBV infection (anti-HBcor). Unfortunately, this observation was also fatal [32].

A publication in Czech indexed in PubMed was the source of an abstract reporting the case of four patients with hematologic oncohematologic diseases in whom hepatitis B reactivation during chemotherapy proceeded as FCH [54]. Three of the patients underwent a successful LT, with good liver function and remission of hematologic disease. The fourth patient died of hepatic failure. However, these observations could not be discussed more in detail owing to the absence of an English version of the article.

Since the early 2000s, reports of the development of FCH in non-oncologic patients have begun to emerge. In 2004, a group of doctors from Australia reported a case of reactivation of chronic hepatitis B in a 29-year-old patient treated with prednisolone (60 mg/day) and chloroquine (250 mg/day) for a mixed connective tissue disease [31]. Fatal hepatic failure developed, and the histologic picture was consistent with FCH. The authors discussed the potential role of both drugs in the development of FCH. Increased HBV replication and intracellular HBV antigen expression in hepatocytes during prednisolone therapy are well-studied. The evidence that chloroquine can reduce the lysis of infected hepatocytes by disrupting normal cellular processing of viral antigens in the liver is less well-known. Importantly, the combination of glucocorticosteroids and hydroxychloroquine was widely used in the treatment of new coronavirus infection at the initial stages of the study of this disease.

The first report on the development of non-transplantation- or HIV-associated FCH C, which was observed in a patient with chronic hepatitis C, was published by researchers from Canada [36]. The patient developed a severe hepatitis with histologic signs of FCH during treatment for glomerulonephritis with cyclophosphamide (150 mg/day orally) and glucocorticosteroids ("pulse therapy" intravenously followed by prednisolone at 50 mg/day orally). The patient died of liver failure. The authors emphasize the possibility of changing the disease pattern from chronic hepatitis to FCH along with IS therapy of autoimmune disease. Furthermore, researchers from Japan have proposed that the distinctive characteristics of immune system reactivity associated with manifest systemic lupus erythematosus may have influenced the progression of HCV infection in an elderly patient, from conventional chronic hepatitis to FCH with cirrhosis [35].

Moreover, doctors from Turkey have reported the development of rapidly progressive liver failure against the background of reactivation of HBV infection in a 55-year-old patient with rheumatoid arthritis after 5 months of therapy with low-dose prednisolone (10 mg/day) and methotrexate (15 mg/week). Lamivudine administration in conjunction with the discontinuation of methotrexate and prednisolone proved to be ineffective. Fortunately, this observation concluded with a successful liver transplantation from a postmortem donor. The authors presented microphotographs of histologic changes in liver tissue characteristic of FCH and an image of a macro preparation of the removed liver with pronounced cholestasis without signs of nodal rearrangement [33].

In recent years, reports on FCH development as part of acute HBV or HCV infection have begun to emerge. In 2019, researchers from India reported a case of acute hepatitis

B (anti-HBcor IgM+) that developed features of FCH in a patient with chronic alcohol intoxication. The diagnosis was confirmed histologically, and treatment with tenofovir was ineffective. A group of physicians from Boston, USA, observed acute hepatitis C (genotype 1a) in an elderly patient who was receiving 25 mg of prednisolone for demyelinating polyneuropathy. The patient's condition was not chronic; however, the physicians observed acute hepatitis C. Treatment with grazoprevir and elbasvir was ineffective, and the patient died 12 days after starting therapy. The histologic picture was consistent with FCH [34].

Three reports on the development of FCH in immunocompetent patients were identified. Physicians from Australia reported the reactivation of HBV infection in a 60-year-old patient who had been receiving long-term therapy with nucleoside analogs (NAs), including adefovir, since 2006, with the addition of telbivudine in 2015, followed by the discontinuation of adefovir in 2017. This resulted in the development of a histologically confirmed clinical picture of FCH. Telbivudine was discontinued, and combination therapy with entecavir and tenofovir was initiated, which proved unsuccessful. Fortunately, LT was performed with a favorable outcome. The authors postulated that the pattern of FCH with the development of FHF is associated with the development of drug resistance when changing antiviral drugs. A case of spontaneous exacerbation of chronic hepatitis B with a histological picture of FCH that ended fatally in a patient treated with program hemodialysis was reported by Wong et al. [22]. Additionally, a Japanese publication indexed in PubMed and available only as an abstract describes the development of FCH C in a 71-year-old patient [21].

Reports of FCH in the context of HBV or HCV infections outside the context of transplantation or HIV are few. This may be due to the limited knowledge of physicians on this pathology or lack of histologic examination of liver tissue in patients who experience infectious hepatitis reactivation during anti-inflammatory therapy for autoimmune diseases. Unfortunately, all the cases described in the literature resulted in fatal outcomes or required LT. Even under modern conditions, when effective drugs are widely available to control HBV infection and eradicate HCV infection, AVT for FCH is not always successful. We believe that there is underdiagnosis (hypodiagnosis) of FCH in patients who underwent bone marrow or solid-organ transplantation, in those receiving various types of IS therapy, and in HIV-infected patients.

TREATMENT AND PROGNOSIS

One of the first reports of the use of lamivudine for the treatment of FCH B in a kidney recipient was by Brind et al. Despite control of viral replication, the patient developed FCH B requiring LT [43]. There are anecdotal reports of successful recovery of liver function in kidney recipients with acute viral hepatitis B as FCH [29, 46]. The high incidence of drug resistance to lamivudine led to the rejection of its widespread use as a first-line AVT for hepatitis B. In a case report, Walsh et al. described the successful use of adefovir in the treatment of FCH in a liver recipient who received combined prophylaxis with specific immunoglobulin (HBIG) and lamivudine for 15 months after LT. The efficacy of adefovir against lamivudine-resistant variants of the virus is clear. However, of interest is the loss of prophylactic efficacy of HBIG after the emergence of a lamivudine-resistant HBV variant. In the removed liver of this patient, who had not received any NA prior to LT, there were 5%–10% of hepatocytes, in which HBsAg was detected by IHS. At 10 months after LT and lamivudine administration, HBsAg became detectable in the recipient's blood. This was observed in 50% of hepatocytes in IHS and in 30% of nuclei and in the cytoplasm of hepatocytes for HBcorAg. At 15 months after LT, jaundice developed. Following successful therapy with adefovir, HBsAg was no longer detected by IHS, whereas HBcorAg was observed in individual nuclei of hepatocytes, but not in the cytoplasm. Lo et al. reported two observations of FCH in liver recipients receiving antiviral prophylaxis with lamivudine. Unfortunately, this group of physicians did not use HBIG until the emergence of lamivudine-resistant strains, which ultimately resulted in liver retransplantation. Following this, combined prophylaxis with adefovir and HBIG was prescribed [81]. As previously stated, the introduction of combined prophylaxis for HBV (HBIG and modern NAs) into routine clinical practice has resulted in a significant reduction in the incidence of FCH B in solid-organ recipients. Consequently, it is currently not possible to evaluate the efficacy of entecavir or tenofovir in the treatment of FCH B. Individual cases of tenofovir use outside the context of transplantation have been unsuccessful [20].

FCH cases observed as a variant of the course of relapsing hepatitis B or C in liver recipients are by far the most studied. In 2010, Narang et al. published a systematic review that included 30 case studies and case series of FCH C in liver recipients [72]. At that time, the only possible AVT option was a combination of interferon (standard or pegylated) and ribavirin. Among the 42 recipients who received AVT, 13 exhibited biochemical and/or virologic responses. Three recipients underwent liver retransplantation, and 19 died. In seven cases, the outcome was not reported. We were the first to report a successful case of a liver recipient cured of FCH C by pegylated interferon monotherapy in Russia [17].

The introduction of DAAs into clinical practice has led to a significant improvement in the efficacy of AVT and prognosis of liver recipients. In a prospective study conducted by Leroy et al., the efficacy of the combination of sofosbuvir and daclatasvir was evaluated in 15 liver recipients with FHC C who received AVT for 24 weeks. In all cases, a complete clinical and virological response was recorded, and no retransplantation was performed [82]. In the same year, Forns et al. published a case analysis of 11 liver recipients with FHC C, included in the SOLAR-1,2 studies, who received a combination of sofosbuvir and ledipasvir with ribavirin for 12 (*n*=7) and 24 (*n*=4) weeks,

respectively. Virus eradication was achieved in all 11 recipients, and clinical improvement was observed in majority of the cases [83]. Further, the combination of simeprevir, sofosbuvir, and ribavirin resulted in viral eradication in 13 liver recipients with FHC C genotype 1 [84].

Unfortunately, modern pangenotypic combinations of DAAs in the treatment of FHC C have not been prospectively studied, and observations are isolated. For example, authors from Italy published two cases of successful use of the combination of glecaprevir and pibrentasvir for 16 weeks after a failed first attempt of sofosbuvir and velpatasvir for 12 weeks. In both cases, FCH occurred as a consequence of HCV and HIV coinfection [85]. Our observations indicate that the combination of sofosbuvir and daclatasvir, administered to a patient infected with genotype 2 virus for 16 weeks, was ineffective. Conversely, the combination of glecaprevir and pibrentasvir, administered as second-line AVT, resulted in success [70]. Unfortunately, in a case report from Japan, FCH progressed rapidly in a kidney recipient, and the combination of glecaprevir and pibrentasvir was unsuccessful. The patient died of hepatic failure [57].

Interestingly, a kidney recipient experienced a recovery from FCH by chance, in the context of allogeneic stem cell (SC) infusion, which was performed after complete withdrawal of IS to prevent kidney transplant rejection. In this case, the patient developed spontaneous bacterial peritonitis and pulmonary infection, in the context of FCH C, which required the cancellation of IS and prescription of antibiotics. The infusion of allogeneic hematopoietic SCs was performed to induce hematopoietic chimerism and kidney transplant tolerance in the recipient. The eradication of HCV RNA in this patient probably resulted from the restoration of the antiviral immune response after the discontinuation of immunosuppressants. The authors discussed other mechanisms involved in recovery, such as transdifferentiation of SCs into functional hepatocytes and/or paracrine effects that promote liver regeneration and suppress local inflammation [56].

Despite the success of viral eradication in the majority of liver recipients with FHC C, fibrosis regresses in only half of these patients. When a repeat graft biopsy was performed 12 months after obtaining a durable virologic response, Mauro et al. noted cirrhosis in 2 (17%) of 12 examined recipients [86]. The results of studies by French physicians are even more disconcerting. A histological analysis of repeated studies conducted 6 months after the completion of AVT (median: 5.3 (0.6–7.4) months) revealed that in 17 liver recipients who underwent FCH and were effectively cured by DAAs, the fibrosis stage increased in 10 patients (59%). Cirrhosis was detected in six patients (35%), and chronic graft rejection developed in four patients (23.5%). The authors concluded that in the case of virus eradication in patients with FCH after LT, fibrosis progression was observed in half of patients, which requires monitoring of fibrosis severity despite HCV cure [87].

CONCLUSIONS

The advent and subsequent integration of contemporary antiviral medications into standard clinical practice for the treatment of HBV and HCV infections has effectively relegated the question of the nature of the course of infectious hepatitis to the category of secondary. In most patients, control of replication (HBV) or eradication (HCV) of the virus from the body is achieved. The exception is a small group of patients with a rapidly progressive course of hepatitis and FHF. Such a course is commonly observed during the use of IS drugs, although it can occur in a various clinical situations. The most typical histologic picture in such cases is massive necrosis and a marked inflammatory reaction. However, there is a subgroup of patients with rapidly progressive viral hepatitis in whom the clinical mask of FHF hides a fundamentally different histologic picture called FCH. We analyzed the publications reporting HBV or HCV reactivation with the development of FHF. The results of histologic examination are understandably rarely reported; sometimes authors cite autopsy findings. This is particularly found in cholestatic disease patterns, where FCH is rarely recognized. Analysis of the literature has shown that despite the presence of effective AVT, the outcomes of FCH are not always favorable. Currently, such a course of hepatitis in recipients of solid organs, primarily the liver, has a favorable prognosis for the patient. For patients from other risk groups, the development of FCH is often fatal.

The observations of FCH not associated with hepatitis B and C viruses are noteworthy. The absence of HBV, HCV, HAV, and HEV and infections in these patients with a characteristic histologic picture of liver disease indicates the development of pathologic changes in the liver, described as FCH, in IS conditions under the influence of various infectious agents.

Currently, the emergence of a large number of drugs selectively acting on the immune system has led to the development of new areas of medicine in hematology, rheumatology, oncology, transplantology, and infectious diseases. However, doctors of these specialties are faced with unexpectedly severe forms of liver damage during specific therapy. Thus, physicians who do not specialize in liver transplantation may be underestimating the potential for FCH development in patients with viral hepatitis B and C. This is particularly true in infectious and internal disease clinics.

ADDITIONAL INFORMATION

Funding source. This article was not supported by any external sources of funding.

Competing interests. The authors declare that they have no competing interests.

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work. V.E. Syutkin — concept development, analysis of literary sources, writing and preparation of text for publication; V.P. Chulanov — analysis of literary sources, writing the text of the article.

REFERENCES

1. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology.* 2018;67(4):1560–1599. doi: 10.1002/hep.29800
2. European Association for the Study of the Liver. EASL 2017. Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(2):370–398. doi: 10.1016/j.jhep.2017.03.021
3. Syutkin VE, Andreytzeva OA, Kozlova AV, Chzhao AV. De novo HBV infection in individuals with a history of liver transplantation due to disease not associated with viral hepatitis B (case analysis). *Infektsionnye bolezni.* 2009;7(4):75–79. (In Russ). EDN: MBDFHV
4. Lenggenhager D, Weber A. Hepatitis E Virus and the Liver: Clinical Settings and Liver Pathology. *Gastroenterology Clinics of North America.* 2017;46(2):393–407. doi:10.1016/j.gtc.2017.01.010
5. Davies SE, Portmann BC, O'Grady JG, et al. Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis. *Hepatology.* 1991;13(1):150–157.
6. O'Grady JG, Smith HM, Davies SE, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications. *J Hepatol.* 1992;14(1):104–111. doi: 10.1016/0168-8278(92)90138-f
7. Schluger LK, Sheiner PA, Thung SN, et al. Severe recurrent cholestatic hepatitis C following orthotopic liver transplantation. *Hepatology.* 1996;23(5):971–976. doi: 10.1002/hep.510230505
8. Lim HL, Lau GK, Davis GL, Dolson, DJ, Lau JY, Cholestatic hepatitis leading to hepatic failure in a patient with organ-transmitted hepatitis C virus infection. *Gastroenterology.* 1994;106(1):248–251. doi: 10.1016/s0016-5085(94)95829-7
9. Duseja A, Nada R, Kalra N, et al. Fibrosing cholestatic hepatitis-like syndrome in a hepatitis B virus and hepatitis C virus-negative renal transplant recipient: a case report with autopsy findings. *Tropical Gastroenterology.* 2003;24(1):31–34.
10. Agarwal SK, Kalra V, Dinda A, et al. Fibrosing cholestatic hepatitis in renal transplant recipient with CMV infection: a case report. *International Urology and Nephrology.* 2004;36(3):433–435. doi: 10.1007/s11255-004-6196-9
11. Duseja A, Das A, Chawla YK, Bhansali A, Sakhuja V. Clinicopathological conference: fibrosing cholestatic hepatitis presenting as subacute hepatic failure in a non-transplant patient. *Dig Dis Sci.* 2009; 54(11):2341–2345. doi: 10.1007/s10620-009-0878-1
12. Muñoz de Bustillo E, Benito A, et al. Fibrosing cholestatic hepatitis-like syndrome in hepatitis B virus-negative and hepatitis C virus-negative renal transplant recipients. *Am J Kidney Dis.* 2001;38(3):640–645. doi: 10.1053/ajkd.2001.26902
13. Shan YS, Lee PC, Wang JR, et al. Fibrosing cholestatic hepatitis possibly related to persistent parvovirus B19 infection in a renal transplant recipient. *Nephrol Dial Transplant.* 2001;16(12): 2420–2422. doi: 10.1093/ndt/16.12.2420
14. Longerich T, Haferkamp K, Tox U, Schirmacher P. Acute liver failure in a renal transplant patient caused by adenoviral hepatitis superimposed on a fibrosing cholestatic hepatitis B. *Human pathology.* 2004;35(7):894–897. doi: 10.1016/j.humpath.2004.04.004
15. Xiao SY, Lu L, Wang HL. Fibrosing cholestatic hepatitis: clinicopathologic spectrum, diagnosis and pathogenesis. *International Journal of Clinical and Experimental Pathology.* 2008;1(5):396–402.
16. Hori T, Onishi Y, Kamei H, et al. Fibrosing cholestatic hepatitis C in post-transplant adult recipients of liver transplantation. *Ann Gastroenterol.* 2016;29(4):454–459. doi: 10.20524/aog.2016.0069
17. Chzhao AV, Andreitseva OI, Syutkin VE, et al. Success of early antiviral monotherapy with pegylated interferon α-2a for posttransplantation fibrosing cholestatic hepatitis C (a clinical case). *Transplantologiya. The Russian Journal of Transplantation.* 2011;(2-3):69–74. (In Russ). doi: 10.23873/2074-0506-2011-0-2-3-69-74
18. De Vera ME, Dvorchik I, Tom K, et al. Survival of liver transplant patients coinfected with HIV and HCV is adversely impacted by recurrent hepatitis C. *Am J Transplant.* 2006;6(12):2983–2993. doi: 10.1111/j.1600-6143.2006.01546.x
19. Sutherland N, Li Wai Suen CFD, Mills C, Lokan J, Sinclair M Fibrosing Cholestatic Hepatitis-Like Syndrome in an Immunocompetent Patient With an Acute Flare of Chronic Hepatitis B. *Hepatology.* 2019;70(4):1480–1483. doi: 10.1002/hep.30763
20. Philips CA, Paramaguru R, Rajesh S, et al. An unusual cause of acute-on-chronic liver failure. *Indian Journal of Gastroenterology.* 2019;38(3):278–279. doi: 10.1007/s12664-019-00963-6
21. Akagi H, Mizuki A, Tominaga T, et al. [Acute hepatitis C infection with prolonged intrahepatic cholestasis and remarkable progression of fibrosis mimicking fibrosing cholestatic hepatitis]. *Nihon Shokakibyo Gakkai Zasshi.* 2014;111(6):1141–1148. (In Japanese).
22. Wong PN, Fung TT, Chan AN, et al. Unusual case of hepatitic cholestasis resembling fibrosing cholestatic hepatitis in a dialysis patient with chronic hepatitis B infection. *J Gastroenterol Hepatol.* 2006;21(10):1635–1637. doi: 10.1111/j.1440-1746.2006.04340.x
23. Fang JW, Wright TL, Lau JY. Fibrosing cholestatic hepatitis in patient with HIV and hepatitis B. *Lancet.* 1993;342(8880):1175. doi: 10.1016/0140-6736(93)92160-u
24. Poulet B, Chapel F, Dény P, et al. Hépatite cholestatique et fibrosante par réactivation virale B au cours du SIDA. *Annales de pathologie.* 1996;16(3):188–191. (In French).
25. Rosenberg PM, Farrell JJ, Abraczinskas DR, et al. Rapidly progressive fibrosing cholestatic hepatitis-hepatitis C virus in HIV coinfection. *Am J Gastroenterol.* 2002;97(2):478–483. doi: 10.1111/j.1572-0241.2002.05459.x
26. Moreno A, Moreno A, Pérez-Elías MJ, et al. Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature. *Human pathology.* 2006;37(10):1344-1349. doi:10.1016/j.humpath.2006.05.003
27. Lee HK, Yoon GS, Min KS, et al. Fibrosing cholestatic hepatitis: a report of three cases. *J Korean Med Sci.* 2000;15(1):111–114. doi: 10.3346/jkms.2000.15.1.111
28. Kojima H, Abei M, Takei N, et al. Fatal reactivation of hepatitis B virus following cytotoxic chemotherapy for acute myelogenous leukemia: fibrosing cholestatic hepatitis. *Eur J Haematol.* 2002; 69(2):101–104. doi: 10.1034/j.1600-0609.2002.02719.x
29. Jung S, Lee HC, Han JM, et al. Four cases of hepatitis B virus-related fibrosing cholestatic hepatitis treated with lamivudine. *J Gastroenterol Hepatol.* 2002;17(3):345–350. doi: 10.1046/j.1440-1746.2002.02600.x
30. Wasmuth JC, Fischer HP, Sauerbruch T, Dumoulin FL. Fatal acute liver failure due to reactivation of hepatitis B following treatment with fludarabine/cyclophosphamide/rituximab for low grade non-Hodgkin's lymphoma. *Eur J Med Res.* 2008;13(10):483–486.
31. Zanati SA, Locarnini SA, Dowling JP, et al. Hepatic failure due to fibrosing cholestatic hepatitis in a patient with pre-surface mutant hepatitis B virus and mixed connective tissue disease treated with prednisolone and chloroquine. *J Clin Virol.* 2004;31(1):53–57. doi: 10.1016/j.jcv.2004.02.013

32. Ceballos-Viro J, López-Picazo JM, Pérez-Gracia JL, et al. Fibrosing cholestatic hepatitis following cytotoxic chemotherapy for small-cell lung cancer. *World J Gastroenterol*. 2009;15(18): 2290–2292. doi: 10.3748/wjg.15.2290
33. Topaloglu S, Calik A, Kalayci O, et al. Fibrosing cholestatic hepatitis after methotrexate and prednisone therapy for rheumatoid arthritis. *Exp Clin Transplant*. 2014;12 Suppl. 1:95–97.
34. Nassar AH, Abdul-Jawad BM, Barnes DS. Hepatic Failure Due to Cholestatic Hepatitis C in an Immunosuppressed Patient Treated With Elbasvir and Grazeprevir. *ACG Case Reports Journal*. 2018;5:e6. doi: 10.14309/crj.2018.6
35. Morii K, Hatono T, Yokoyama M, et al., Fibrosing Cholestatic Hepatitis C in a Patient with Systemic Lupus Erythematosus. *J Gastroenterol Hepatol Res*. 2012;1(8):165–170.
36. Saleh F, Ko HH, Davis JE, et al. Fatal hepatitis C associated fibrosing cholestatic hepatitis as a complication of cyclophosphamide and corticosteroid treatment of active glomerulonephritis. *Ann Hepatol*. 2007;6(3):186–189.
37. Pellicelli AM, D'ambrosio C, Dessanti ML, et al. Cholestatic hepatitis C after chemotherapy containing rituximab in diffuse large B cell lymphoma. *Ann Hepatol*. 2015;14(5):756–761.
38. Chen CH, Chen PJ, Chu JS, et al. Fibrosing cholestatic hepatitis in a hepatitis B surface antigen carrier after renal transplantation. *Gastroenterology*. 1994;107(5):1514–1518. doi: 10.1016/0016-5085(94)90557-6
39. Hung YB, Liang JT, Chu JS, Chen KM, Lee CS. Fulminant hepatic failure in a renal transplant recipient with positive hepatitis B surface antigens: a case report of fibrosing cholestatic hepatitis. *Hepatogastroenterology*. 1995;42(6):913–918.
40. Booth JC, Goldin RD, Brown JL, Karayiannis P, Thomas HC. Fibrosing cholestatic hepatitis in a renal transplant recipient associated with the hepatitis B virus precore mutant. *J Hepatol*. 1995.22(4):500–503. doi: 10.1016/0168-8278(95)80116-2
41. Al Faraidy K, Yoshida EM, Davis JE, et al. Alteration of the dismal natural history of fibrosing cholestatic hepatitis secondary to hepatitis B virus with the use of lamivudine. *Transplantation*. 1997;64(6): 926–928. doi: 10.1097/00007890-199709270-00024
42. Lam PW, Wachs ME, Somberg KA, et al. Fibrosing cholestatic hepatitis in renal transplant recipients. *Transplantation*. 1996;61(3):378–381. doi: 10.1097/00007890-199602150-00008
43. Brind AM, Bennett MK, Bassendine MF. Nucleoside analogue therapy in fibrosing cholestatic hepatitis — a case report in an HBsAg positive renal transplant recipient. *Liver*. 1998;18(2):134–139. doi: 10.1111/j.1600-0676.1998.tb00139.x
44. Waguri N, Ichida T, Fujimaki R, et al. Fibrosing cholestatic hepatitis after living related-donor renal transplantation. *J Gastroenterol Hepatol*. 1998;13(11):1133–1137. doi: 10.1111/j.1440-1746.1998.tb00589.x
45. Toth CM, Pascual M, Chung RT, et al. Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy. *Transplantation*. 1998;66(9):1254–1258. doi: 10.1097/00007890-199811150-00023
46. Chan TM, Wu PC, Li FK, et al. Treatment of fibrosing cholestatic hepatitis with lamivudine. *Gastroenterology*. 1998;115(1):177–181. doi: 10.1016/s0016-5085(98)70380-4
47. Zylberberg H, Carnot F, Mamzer MF, et al. Hepatitis C virus-related fibrosing cholestatic hepatitis after renal transplantation. *Transplantation*. 1997;63(1):158–160. doi: 10.1097/00007890-199701150-00029
48. Muñoz De Bustillo E, Ibarrola C, Colina F, et al. Fibrosing cholestatic hepatitis in hepatitis C virus-infected renal transplant recipients. *J Am Soc Nephrol*. 1998;9(6):1109–1113. doi: 10.1681/ASN.V961109
49. Delladetsima JK, Boletis JN, Makris F, et al. Fibrosing cholestatic hepatitis in renal transplant recipients with hepatitis C virus infection. *Liver Transpl Surg*. 1999;5(4):294–300. doi: 10.1002/lt.500050417
50. Delladetsima I, Psichogiou M, Sypsa V, et al. The course of hepatitis C virus infection in pretransplantation anti-hepatitis C virus-negative renal transplant recipients: a retrospective follow-up study. *Am J Kidney Dis*. 2006:47(2):309–316. doi: 10.1053/j.ajkd.2005.11.008
51. Boletis JN, Delladetsima JK, Makris F, et al. Cholestatic syndromes in renal transplant recipients with HCV infection. *Transpl Int*. 2000;13 Suppl. 1:S375–S379. doi: 10.1007/s001470050365
52. Hooda AK, Puri P, Narula AS, et al. Hepatitis C virus-related fibrosing cholestatic hepatitis in a renal transplant recipient. *Indian J Gastroenterol*. 2006;25(6):308–309.
53. Shores NJ, Kimberly J. Seronegative hepatitis C-related fibrosing cholestatic hepatitis after renal transplant: a case report and review of the literature. *NDT Plus*. 2008;1(4):241–243. doi: 10.1093/ndtplus/sfn027
54. Honsová E, Sperl J. Fibrotizující cholestatická hepatitida — onemocneni nejen transplantovaných pacientů. *Ceskoslovenska patologie*. 2011;47(2):55–58. (In Czech).
55. Siddiqui AR, Abbas Z, Luck NH, et al. Experience of fibrosing cholestatic hepatitis with hepatitis C virus in kidney transplant recipients. *Transplant Proc*. 2012;44(3):721–724. doi: 10.1016/j.transproceed.2011.12.019
56. Li DL, Fang J, Zheng Z, Wu W, Wu Z. Successful treatment of fibrosing cholestatic hepatitis following kidney transplantation with allogeneic hematopoietic stem cell transplantation: a case report. *Medicine*. 2015;94(5):e480. doi: 10.1097/MD.0000000000000480
57. Shinzato T, Kubo T, Shimizu T, Nanmoku K, Yagisawa T. Fibrosing cholestatic hepatitis in a kidney transplant recipient with hepatitis C virus. *CEN Case Reports*. 2019;8(2):101–105. doi: 10.1007/s13730-018-0374-6
58. Kapila N, Al-Khalloufi K, Bejarano PA, Vanatta JM, Zervos XB. Fibrosing cholestatic hepatitis after kidney transplantation from HCV-viremic donors to HCV-negative recipients: A unique complication in the DAA era. *Am J Transplant*. 2020;20(2):600–605. doi: 10.1111/ajt.15583
59. Delgado J, Muñoz de Bustillo E, Ibarrola C, et al. Hepatitis C virus-related fibrosing cholestatic hepatitis after cardiac transplantation: is azathioprine a contributory factor? *J Heart Lung Transplant*. 1999;18(6):607–610. doi: 10.1016/s1053-2498(98)00019-9
60. Ong JP, Barnes DS, Younossi ZM, et al. Outcome of de novo hepatitis C virus infection in heart transplant recipients. *Hepatology*. 1999;30(5):1293–1298. doi: 10.1002/hep.510300519
61. Liu CH, Chen YS, Wang SS, Kao JH. Treatment of de novo hepatitis C virus-related fibrosing cholestatic hepatitis after orthotopic heart transplantation by ledipasvir and sofosbuvir. *J Formos Med Assoc*. 2017;116(5):407–409. doi: 10.1016/j.jfma.2016.12.005
62. Mcivor C, Morton J, Bryant A, et al. Fatal reactivation of precore mutant hepatitis B virus associated with fibrosing cholestatic hepatitis after bone marrow transplantation. *Ann Intern Med*. 1994;121(4): 274–275. doi: 10.7326/0003-4819-121-4-199408150-00007
63. Suresh RL, Merican I, Chang KM, Yong SM, Purusothaman V. Cholestatic fibrosing hepatitis and hepatitis B after bone marrow transplantation. *The Medical Journal of Malaysia*. 2001;56(4):508–511.
64. Evans AT, Loeb KR, Shulman HM, Hassan S, Qiu WC, Hockenbery DM et al. Fibrosing cholestatic hepatitis C after hematopoietic cell transplantation: report of 3 fatal cases. *The American Journal of Surgical Pathology*. 2015;39(2):212–220. doi: 10.1097/PAS.0000000000000345

65. Wiesner RH, Sorrell M, Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C. *Liver Transpl*. 2003;9(11):S1–S9. doi: 10.1053/jlts.2003.50268
66. Verna EC, Abdelmessih R, Salomao MA, et al. Cholestatic hepatitis C following liver transplantation: an outcome-based histological definition, clinical predictors, and prognosis. *Liver Transpl*. 2013;19(1):78–88. doi: 10.1002/lt.23559
67. Moreira RK, Salomao M, Verna EC, Brown RS Jr, Lefkowitch JH. The Hepatitis Aggressiveness Score (HAS): a novel classification system for post-liver transplantation recurrent hepatitis C. *The American Journal of Surgical Pathology*. 2013;37(1):104–113. doi: 10.1097/PAS.0b013e31826a92ac
68. Berenguer M, McCaughan G. Hepatitis C virus-associated cholestatic hepatitis: we cannot seem to agree on diagnostic criteria. *Liver Transpl*. 2013;19(2):115–117. doi: 10.1002/lt.23580
69. Lucey MR, Graham DM, Martin P, et al. Recurrence of hepatitis B and delta hepatitis after orthotopic liver transplantation. *Gut*. 1992;33(10):1390–1396. doi: 10.1136/gut.33.10.1390
70. Voskanyan SE, Syutkin VE, Shabalin MV, et al. Seronegative fibrosing cholestatic hepatitis C after liver retransplantation for unresectable neuroendocrine tumor liver metastases. *Transplantologiya. The Russian Journal of Transplantation*. 2020;12(4):319–331. (In Russ). doi: 10.23873/2074-0506-2020-12-4-319-331
71. McCaughan GW, Bowen DG. Pathogenesis of cholestatic hepatitis C. *J Hepatol*. 2011;54(2):392–394. doi: 10.1016/j.jhep.2010.09.010
72. Narang TK, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. *Liver Transpl*. 2010;16(11):1228–1235. doi: 10.1002/lt.22175
73. Angus PW, Locarnini SA, McCaughan GW, et al. Hepatitis B virus precore mutant infection is associated with severe recurrent disease after liver transplantation. *Hepatology*. 1995;21(1):14–18.
74. Fang JW, Tung FY, Davis GL, et al. Fibrosing cholestatic hepatitis in a transplant recipient with hepatitis B virus precore mutant. *Gastroenterology*. 1993;105(3):901–904. doi: 10.1016/0016-5085(93)90910-5
75. Bonino F, Brunetto MR. Hepatitis B virus heterogeneity, one of many factors influencing the severity of hepatitis B. *J Hepatol*. 1993;18(1):5–8. doi: 10.1016/s0168-8278(05)80003-0
76. Cooksley WG, McIvor CA. Fibrosing cholestatic hepatitis and HBV after bone marrow transplantation. *Biomed Pharmacother*. 1995;49(3):117–124. doi: 10.1016/0753-3322(96)82604-7
77. Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology*. 2009;49 Suppl. 5:S138–S145. doi: 10.1002/hep.22883
78. Revill PA, Littlejohn M, Ayres A et al. Identification of a novel hepatitis B virus precore/core deletion mutant in HIV/hepatitis B virus co-infected individuals. *AIDS*. 2007;21(13):1701–1710. doi: 10.1097/QAD.0b013e32826fb305
79. Eyster ME, Fried MW, Di Bisceglie AM, Goedert JJ. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study. *Blood*. 1994;84(4):1020–1023.
80. Walsh KM, Woodall T, Lamy P, et al. Successful treatment with adefovir dipivoxil in a patient with fibrosing cholestatic hepatitis and lamivudine resistant hepatitis B virus. *Gut*. 2001;49(3):436–440. doi: 10.1136/gut.49.3.436
81. Lo CM, Cheung ST, Ng IOL, et al. Fibrosing cholestatic hepatitis secondary to precore/core promoter hepatitis B variant with lamivudine resistance: successful retransplantation with combination adefovir dipivoxil and hepatitis B immunoglobulin. *Liver Transpl*. 2004;10(4):557–563. doi: 10.1002/lt.20133
82. Leroy V, Dumortier J, Coilly A, Sebagh M, Fougerou-Leurent C, Radenne S et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation. *Clin Gastroenterol Hepatol*. 2015;13(11):1993–2001. doi: 10.1016/j.cgh.2015.05.030
83. Forns X, Mutimer D, Manns M, et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of fibrosing cholestatic hepatitis C after liver transplantation. *J Hepatol*. 2015;62 Suppl. 2:S623–S623. doi: 10.1016/S0168-8278(15)30982-X
84. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology*. 2015;61(6):1880–1886. doi: 10.1002/hep.27770
85. Merli M, Rossotti R, Travi G, et al. Sustained virological response with 16-week glecaprevir/pibrentasvir after failure to sofosbuvir/velpatasvir in post-transplant severe HCV recurrence in HIV. *Transpl Infect Dis*. 2019;21(6):e13165. doi: 10.1111/tid.13165
86. Mauro E, Crespo G, Montironi C, et al. Viral eradication and fibrosis resolution in post-liver transplant cholestatic hepatitis C virus. *Liver Transpl*. 2018;24(5):703–707. doi: 10.1002/lt.25027
87. Coilly A, Sebagh M, Fougerou-Leurent C, et al. HCV eradication does not protect from fibrosis progression in patients with fibrosing cholestatic hepatitis after liver transplantation. *Clinics and Research in Hepatology and Gastroenterology*. 2022;46(9):102024. doi: 10.1016/j.clinre.2022.102024

СПИСОК ЛИТЕРАТУРЫ

1. Terrault N.A., Lok A.S.F., McMahon B.J., et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance // Hepatology. 2018. Vol. 67, N 4. P. 1560–1599. doi: 10.1002/hep.29800
2. European Association for the Study of the Liver. EASL 2017. Clinical Practice Guidelines on the management of hepatitis B virus infection // J Hepatol. 2017. Vol. 67, N 2. P. 370–398. doi: 10.1016/j.jhep.2017.03.021
3. Сюткин В.Е., Андрейцева О.И., Козлова А.В.,Чжао А.В. Инфекция HBV, возникшая de novo у лиц, перенёсших трансплантацию печени в связи с заболеванием, не связанным с вирусным гепатитом В (анализ серии случаев) // Инфекционные болезни. 2009. Т. 7, № 4. С. 75–79. EDN: MBDFHV
4. Lenggenhager D., Weber A. Hepatitis E Virus and the Liver: Clinical Settings and Liver Pathology // Gastroenterology Clinics of North America. 2017. Vol. 46, N 2. P. 393–407. doi: 10.1016/j.gtc.2017.01.010
5. Davies S.E., Portmann B.C., O'Grady J.G., et al. Hepatic histological findings after transplantation for chronic hepatitis B virus infection, including a unique pattern of fibrosing cholestatic hepatitis // Hepatology. 1991. Vol. 13, N 1. P. 150–157.
6. O'Grady J.G., Smith H.M., Davies S.E., et al. Hepatitis B virus reinfection after orthotopic liver transplantation. Serological and clinical implications // J Hepatol. 1992. Vol. 14, N 1. P. 104–111. doi: 10.1016/0168-8278(92)90138-f
7. Schluger L.K., Sheiner P.A., Thung S.N., et al. Severe recurrent cholestatic hepatitis C following orthotopic liver

transplantation // Hepatology. 1996. Vol. 23, N 5. P. 971–976. doi: 10.1002/hep.510230505

8. Lim H.L., Lau G.K., Davis G.L., Dolson D.J., Lau J. Y. Cholestatic hepatitis leading to hepatic failure in a patient with organ-transmitted hepatitis C virus infection // Gastroenterology. 1994. Vol. 106, N 1. P. 248–251. doi: 10.1016/s0016-5085(94)95829-7

9. Duseja A., Nada R., Kalra N., et al. Fibrosing cholestatic hepatitis-like syndrome in a hepatitis B virus and hepatitis C virus-negative renal transplant recipient: a case report with autopsy findings // Tropical Gastroenterology. 2003. Vol. 24, N 1. P. 31–34.

10. Agarwal S.K., Kalra V., Dinda A., et al. Fibrosing cholestatic hepatitis in renal transplant recipient with CMV infection: a case report // International Urology and Nephrology. 2004. Vol. 36, N 3. P. 433–435. doi: 10.1007/s11255-004-6196-9

11. Duseja A., Das A., Chawla Y.K, Bhansali A., Sakhuja V. Clinicopathological conference: fibrosing cholestatic hepatitis presenting as subacute hepatic failure in a non-transplant patient // Dig Dis Sci. 2009. Vol. 54, N 11. P. 2341–2345. doi: 10.1007/s10620-009-0878-1

12. Muñoz de Bustillo E., Benito A., Colina F., et al. Fibrosing cholestatic hepatitis-like syndrome in hepatitis B virus-negative and hepatitis C virus-negative renal transplant recipients // Am J Kidney Dis. 2001. Vol. 38, N 3. P. 640–645. doi: 10.1053/ajkd.2001.26902

13. Shan Y.S., Lee P.C., Wang J.R., et al. Fibrosing cholestatic hepatitis possibly related to persistent parvovirus B19 infection in a renal transplant recipient // Nephrol Dial Transplant. 2001. Vol. 16, N 12. P. 2420–2422. doi: 10.1093/ndt/16.12.2420

14. Longerich T., Haferkamp K., Tox U., Schirmacher P. Acute liver failure in a renal transplant patient caused by adenoviral hepatitis superimposed on a fibrosing cholestatic hepatitis B // Human Pathology. 2004. Vol. 35, N 7. P. 894–897. doi: 10.1016/j.humpath.2004.04.004

15. Xiao S.Y., Lu L., Wang H.L. Fibrosing cholestatic hepatitis: clinicopathologic spectrum, diagnosis and pathogenesis // International Journal of Clinical and Experimental Pathology. 2008. Vol. 1, N 5. P. 396–402.

16. Hori T., Onishi Y., Kamei H., et al. Fibrosing cholestatic hepatitis C in post-transplant adult recipients of liver transplantation // Ann Gastroenterol. 2016. Vol. 29, N 4. P. 454–459. doi: 10.20524/aog.2016.0069

17. Чжао А.В., Андрейцева О.И., Сюткин В.Е., и др. Успех ранней противовирусной монотерапии пегилированным интерфероном альфа-2а посттрансплантационного фиброзирующего холестатического гепатита С (клиническое наблюдение) // Трансплантология. 2011. № 2-3. С. 69–74. doi: 10.23873/2074-0506-2011-0-2-3-69-74

18. De Vera M.E., Dvorchik I., Tom K., et al. Survival of liver transplant patients coinfected with HIV and HCV is adversely impacted by recurrent hepatitis C // Am J Transplant. 2006. Vol. 6, N 12. P. 2983–2993. doi: 10.1111/j.1600-6143.2006.01546.x

19. Sutherland N., Li Wai Suen C.F.D., Mills C., Lokan J., Sinclair M. Fibrosing Cholestatic Hepatitis-Like Syndrome in an Immunocompetent Patient With an Acute Flare of Chronic Hepatitis B // Hepatology. 2019. Vol. 70, N 4. P. 1480–1483. doi: 10.1002/hep.30763

20. Philips C.A., Paramaguru R., Rajesh S., et al. An unusual cause of acute-on-chronic liver failure // Indian Journal of Gastroenterology. 2019. Vol. 38, N 3. P. 278–279. doi: 10.1007/s12664-019-00963-6

21. Akagi H., Mizuki A., Tominaga T., et al. [Acute hepatitis C infection with prolonged intrahepatic cholestasis and remarkable progression of fibrosis mimicking fibrosing cholestatic hepatitis] // Nihon Shokakibyo Gakkai Zasshi. 2014. Vol. 111, N 6. P. 1141–1148.

22. Wong P.N., Fung T.T., Chan A.N., et al. Unusual case of hepatitic cholestasis resembling fibrosing cholestatic hepatitis in a dialysis patient with chronic hepatitis B infection // J Gastroenterol Hepatol. 2006. Vol. 21, N 10. P. 1635–1637. doi: 10.1111/j.1440-1746.2006.04340.x

23. Fang J.W., Wright T.L., Lau J.Y. Fibrosing cholestatic hepatitis in patient with HIV and hepatitis B // Lancet. 1993. Vol. 342, N 8880. P. 1175. doi: 10.1016/0140-6736(93)92160-u

24. Poulet B., Chapel F., Dény P., et al. Hépatite cholestatique et fibrosante par réactivation virale B au cours du SIDA // Annales de pathologie. 1996. Vol. 16, N 3. P. 188–191.

25. Rosenberg P.M., Farrell J.J., Abraczinskas D.R., et al. Rapidly progressive fibrosing cholestatic hepatitis-hepatitis C virus in HIV coinfection // Am J Gastroenterol. 2002. Vol. 97, N 2. P. 478–483. doi: 10.1111/j.1572-0241.2002.05459.x

26. Moreno A., Moreno A., Pérez-Elías M.J., et al. Syncytial giant cell hepatitis in human immunodeficiency virus-infected patients with chronic hepatitis C: 2 cases and review of the literature // Human pathology. 2006. Vol. 37, N 10. P. 1344–1349. doi: 10.1016/j.humpath.2006.05.003

27. Lee H.K., Yoon G.S., Min K.S., et al. Fibrosing cholestatic hepatitis: a report of three cases // J Korean Med Sci. 2000. Vol. 15, N 1. P. 111–114. doi: 10.3346/jkms.2000.15.1.111

28. Kojima H., Abei M., Takei N., et al. Fatal reactivation of hepatitis B virus following cytotoxic chemotherapy for acute myelogenous leukemia: fibrosing cholestatic hepatitis // Eur J Haematol. 2002. Vol. 69, N 2. P. 101–104. doi: 10.1034/j.1600-0609.2002.02719.x

29. Jung S., Lee H.C., Han J.M., et al. Four cases of hepatitis B virus-related fibrosing cholestatic hepatitis treated with lamivudine // J Gastroenterol Hepatol. 2002. Vol. 17, N 3. P. 345–350. doi: 10.1046/j.1440-1746.2002.02600.x

30. Wasmuth J.-C., Fischer H.-P., Sauerbruch T., Dumoulin F.L. Fatal acute liver failure due to reactivation of hepatitis B following treatment with fludarabine/cyclophosphamide/rituximab for low grade non-Hodgkin's lymphoma // Eur J Med Res. 2008. Vol. 13, N 10. P. 483–486.

31. Zanati S.A., Locarnini S.A., Dowling J.P., et al. Hepatic failure due to fibrosing cholestatic hepatitis in a patient with pre-surface mutant hepatitis B virus and mixed connective tissue disease treated with prednisolone and chloroquine // J Clin Virol. 2004. Vol. 31, N 1. P. 53–57. doi: 10.1016/j.jcv.2004.02.013

32. Ceballos-Viro J., López-Picazo J.M., Pérez-Gracia J.L., et al. Fibrosing cholestatic hepatitis following cytotoxic chemotherapy for small-cell lung cancer // World J Gastroenterol. 2009. Vol. 15, N 18. P. 2290–2292. doi: 10.3748/wjg.15.2290

33. Topaloglu S., Calik A., Kalayci O., et al. Fibrosing cholestatic hepatitis after methotrexate and prednisone therapy for rheumatoid arthritis // Exp Clin Transplant. 2014. Vol. 12, Suppl. 1. P. 95–97.

34. Nassar A.H., Abdul-Jawad B.M., Barnes D.S. Hepatic Failure Due to Cholestatic Hepatitis C in an Immunosuppressed Patient Treated With Elbasvir and Grazeprevir // ACG Case Reports Journal. 2018. Vol. 5. P. e6. doi: 10.14309/crj.2018.6

35. Morii K., Hatono T., Yokoyama M., et al. Fibrosing Cholestatic Hepatitis C in a Patient with Systemic Lupus Erythematosus // J Gastroenterol Hepatol Res. 2012. Vol. 1, N 8. P. 165–170.

36. Saleh F., Ko H.H., Davis J.E., et al. Fatal hepatitis C associated fibrosing cholestatic hepatitis as a complication of cyclophosphamide and corticosteroid treatment of active glomerulonephritis // Ann Hepatol. 2007. Vol. 6, N 3. P. 186–189.
37. Pellicelli A.M., D'ambrosio C., Dessanti M.L., et al. Cholestatic hepatitis C after chemotherapy containing rituximab in diffuse large B cell lymphoma // Ann Hepatol. 2015. Vol. 14, N 5. P. 756–761.
38. Chen C.H., Chen P.J., Chu J.S., et al. Fibrosing cholestatic hepatitis in a hepatitis B surface antigen carrier after renal transplantation // Gastroenterology. 1994. Vol. 107, N 5. P. 1514–1518. doi: 10.1016/0016-5085(94)90557-6
39. Hung Y.B., Liang J.T., Chu J.S., Chen K.M., Lee C.S. Fulminant hepatic failure in a renal transplant recipient with positive hepatitis B surface antigens: a case report of fibrosing cholestatic hepatitis // Hepatogastroenterology. 1995. Vol. 42, N 6. P. 913–918.
40. Booth J.C., Goldin R.D., Brown J.L., Karayiannis P., Thomas H.C. Fibrosing cholestatic hepatitis in a renal transplant recipient associated with the hepatitis B virus precore mutant // J Hepatol. 1995. Vol. 22, N 4. P. 500–503. doi: 10.1016/0168-8278(95)80116-2
41. Al Faraidy K., Yoshida E.M., Davis J.E., et al. Alteration of the dismal natural history of fibrosing cholestatic hepatitis secondary to hepatitis B virus with the use of lamivudine // Transplantation. 1997. Vol. 64, N 6. P. 926–928. doi: 10.1097/00007890-199709270-00024
42. Lam P.W., Wachs M.E., Somberg K.A., et al. Fibrosing cholestatic hepatitis in renal transplant recipients // Transplantation. 1996. Vol. 61, N 3. P. 378–381. doi: 10.1097/00007890-199602150-00008
43. Brind A.M., Bennett M.K., Bassendine M.F. Nucleoside analogue therapy in fibrosing cholestatic hepatitis — a case report in an HBsAg positive renal transplant recipient // Liver. 1998. Vol. 18, N 2. P. 134–139. doi: 10.1111/j.1600-0676.1998.tb00139.x
44. Waguri N., Ichida T., Fujimaki R., et al. Fibrosing cholestatic hepatitis after living related-donor renal transplantation // J Gastroenterol Hepatol. 1998. Vol. 13, N 11. P. 1133–1137. doi: 10.1111/j.1440-1746.1998.tb00589.x
45. Toth C.M., Pascual M., Chung R.T., et al. Hepatitis C virus-associated fibrosing cholestatic hepatitis after renal transplantation: response to interferon-alpha therapy // Transplantation. 1998. Vol. 66, N 9. P. 1254–1258. doi: 10.1097/00007890-199811150-00023
46. Chan T.M., Wu P.C., Li F.K., et al. Treatment of fibrosing cholestatic hepatitis with lamivudine // Gastroenterology. 1998. Vol. 115, N 1. P. 177–181. doi: 10.1016/s0016-5085(98)70380-4
47. Zylberberg H., Carnot F., Mamzer M.F., et al. Hepatitis C virus-related fibrosing cholestatic hepatitis after renal transplantation // Transplantation. 1997. Vol. 63, N 1. P. 158–160. doi: 10.1097/00007890-199701150-00029
48. Muñoz De Bustillo E., Ibarrola C., Colina F., et al. Fibrosing cholestatic hepatitis in hepatitis C virus-infected renal transplant recipients // J Am Soc Nephrol. 1998. Vol. 9, N 6. P. 1109–1113. doi: 10.1681/ASN.V961109
49. Delladetsima J.K., Boletis J.N., Makris F., et al. Fibrosing cholestatic hepatitis in renal transplant recipients with hepatitis C virus infection // Liver Transpl Surg. 1999. Vol. 5, N 4. P. 294–300. doi: 10.1002/lt.500050417
50. Delladetsima I., Psichogiou M., Sypsa V., et al. The course of hepatitis C virus infection in pretransplantation anti-hepatitis C virus-negative renal transplant recipients: a retrospective follow-up study // Am J Kidney Dis. 2006. Vol. 47, N 2. P. 309–316. doi: 10.1053/j.ajkd.2005.11.008
51. Boletis J.N., Delladetsima J.K., Makris F., et al. Cholestatic syndromes in renal transplant recipients with HCV infection // Transpl Int. 2000. Vol. 13, Suppl. 1. P. S375–S379. doi: 10.1007/s001470050365
52. Hooda A.K., Puri P., Narula A.S., et al. Hepatitis C virus-related fibrosing cholestatic hepatitis in a renal transplant recipient // Indian J Gastroenterol. 2006. Vol. 25, N 6. P. 308–309.
53. Shores N.J., Kimberly J. Seronegative hepatitis C-related fibrosing cholestatic hepatitis after renal transplant: a case report and review of the literature // NDT Plus. 2008. Vol. 1, N 4. P. 241–243. doi: 10.1093/ndtplus/sfn027
54. Honsová E., Sperl J. Fibrotizující cholestatická hepatitida — onemocneni nejen transplantovaných pacientů // Ceskoslovenska patologie. 2011. Vol. 47, N 2. P. 55–58.
55. Siddiqui A.R., Abbas Z., Luck N.H., et al. Experience of fibrosing cholestatic hepatitis with hepatitis C virus in kidney transplant recipients // Transplant Proc. 2012. Vol. 44, N 3. P. 721–724. doi: 10.1016/j.transproceed.2011.12.019
56. Li D.L., Fang J., Zheng Z., Wu W., Wu Z. Successful treatment of fibrosing cholestatic hepatitis following kidney transplantation with allogeneic hematopoietic stem cell transplantation: a case report // Medicine. 2015. Vol. 94, N 5. P. e480. doi: 10.1097/MD.0000000000000480
57. Shinzato T., Kubo T., Shimizu T., Nanmoku K., Yagisawa T. Fibrosing cholestatic hepatitis in a kidney transplant recipient with hepatitis C virus // CEN Case Reports. 2019. Vol. 8, N 2. P. 101–105. doi: 10.1007/s13730-018-0374-6
58. Kapila N., Al-Khalloufi K., Bejarano P.A., Vanatta J.M., Zervos X.B. Fibrosing cholestatic hepatitis after kidney transplantation from HCV-viremic donors to HCV-negative recipients: A unique complication in the DAA era // Am J Transplant. 2020. Vol. 20, N 2. P. 600–605. doi: 10.1111/ajt.15583
59. Delgado J., Muñoz de Bustillo E., Ibarrola C., et al. Hepatitis C virus-related fibrosing cholestatic hepatitis after cardiac transplantation: is azathioprine a contributory factor? // J Heart Lung Transplant. 1999. Vol. 18, N 6. P. 607–610. doi: 10.1016/s1053-2498(98)00019-9
60. Ong J.P., Barnes D.S., Younossi Z.M., et al. Outcome of de novo hepatitis C virus infection in heart transplant recipients // Hepatology. 1999. Vol. 30, N 5. P. 1293–1298. doi: 10.1002/hep.510300519
61. Liu C.-H., Chen Y.-S., Wang S.-S., Kao J-.H. Treatment of de novo hepatitis C virus-related fibrosing cholestatic hepatitis after orthotopic heart transplantation by ledipasvir and sofosbuvir // J Formos Med Assoc. 2017. Vol. 116, N 5. P. 407–409. doi: 10.1016/j.jfma.2016.12.005
62. McIvor C., Morton J., Bryant A., et al. Fatal reactivation of precore mutant hepatitis B virus associated with fibrosing cholestatic hepatitis after bone marrow transplantation // Ann Intern Med. 1994. Vol. 121, N 4. P. 274–275. doi: 10.7326/0003-4819-121-4-199408150-00007
63. Suresh R.L., Merican I., Chang K.M., Yong S.M., Purusothaman V. Cholestatic fibrosing hepatitis and hepatitis B after bone marrow transplantation // The Medical Journal of Malaysia. 2001. Vol. 56, N 4. P. 508–511.
64. Evans A.T., Loeb K.R., Shulman H.M., et al. Fibrosing cholestatic hepatitis C after hematopoietic cell transplantation: report of 3 fatal cases // The American Journal of Surgical Pathology. 2015. Vol. 39, N 2. P. 212–220. doi: 10.1097/PAS.0000000000000345
65. Wiesner R.H., Sorrell M., Villamil F. Report of the first International Liver Transplantation Society expert panel consensus conference on liver transplantation and hepatitis C // Liver Transpl. 2003. Vol. 9, N 11. P. S1–S9. doi: 10.1053/jlts.2003.50268
66. Verna E.C., Abdelmessih R., Salomao M.A., et al. Cholestatic hepatitis C following liver transplantation: an outcome-based

histological definition, clinical predictors, and prognosis // Liver Transpl. 2013. Vol. 19, N 1. P. 78–88. doi: 10.1002/lt.23559
67. Moreira R.K., Salomao M., Verna E.C., Brown R.S. Jr., Lefkowitch J.H. The Hepatitis Aggressiveness Score (HAS): a novel classification system for post-liver transplantation recurrent hepatitis C // The American Journal of Surgical Pathology. 2013. Vol. 37, N 1. P. 104–113. doi: 10.1097/PAS.0b013e31826a92ac
68. Berenguer M., McCaughan G. Hepatitis C virus-associated cholestatic hepatitis: we cannot seem to agree on diagnostic criteria // Liver Transpl. 2013. Vol. 19, N 2. P. 115–117. doi: 10.1002/lt.23580
69. Lucey M.R., Graham D.M., Martin P., et al. Recurrence of hepatitis B and delta hepatitis after orthotopic liver transplantation // Gut. 1992. Vol. 33, N 10. P. 1390–1396. doi: 10.1136/gut.33.10.1390
70. Восканян С.Э., Сюткин В.Е., Шабалин М.В., и др. Серонегативный фиброзирующий холестатический гепатит С после ретрансплантации печени, проведённой по поводу нерезектабельных метастазов нейроэндокринного рака тонкой кишки // Трансплантология. 2020. Т. 12, № 4. С. 319–331. doi: 10.23873/2074-0506-2020-12-4-319-331
71. McCaughan G.W., Bowen D.G. Pathogenesis of cholestatic hepatitis C // J Hepatol. 2011. Vol. 54, N 2. P. 392–394. doi: 10.1016/j.jhep.2010.09.010
72. Narang T.K., Ahrens W., Russo M.W. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria // Liver Transpl. 2010. Vol. 16, N 11. P. 1228–1235. doi: 10.1002/lt.22175
73. Angus P.W., Locarnini S.A., McCaughan G.W., et al. Hepatitis B virus precore mutant infection is associated with severe recurrent disease after liver transplantation // Hepatology. 1995. Vol. 21, N 1. P. 14–18.
74. Fang J.W., Tung F.Y., Davis G.L., et al. Fibrosing cholestatic hepatitis in a transplant recipient with hepatitis B virus precore mutant // Gastroenterology. 1993. Vol. 105, N 3. P. 901–904. doi: 10.1016/0016-5085(93)90910-5
75. Bonino F., Brunetto M.R. Hepatitis B virus heterogeneity, one of many factors influencing the severity of hepatitis B // J Hepatol. 1993. Vol. 18, N 1. P. 5–8. doi: 10.1016/s0168-8278(05)80003-0
76. Cooksley W.G., McIvor C.A. Fibrosing cholestatic hepatitis and HBV after bone marrow transplantation // Biomed Pharmacother. 1995. Vol. 49, N 3. P. 117–124. doi: 10.1016/0753-3322(96)82604-7
77. Thio C.L. Hepatitis B and human immunodeficiency virus coinfection // Hepatology. 2009. Vol. 49, Suppl. 5. P. S138–S145. doi: 10.1002/hep.22883
78. Revill P.A., Littlejohn M., Ayres A., et al. Identification of a novel hepatitis B virus precore/core deletion mutant in HIV/hepatitis B virus co-infected individuals // AIDS. 2007. Vol. 21, N 13. P. 1701–1710. doi: 10.1097/QAD.0b013e32826fb305
79. Eyster M.E., Fried M.W., Di Bisceglie A.M., Goedert J.J. Increasing hepatitis C virus RNA levels in hemophiliacs: relationship to human immunodeficiency virus infection and liver disease. Multicenter Hemophilia Cohort Study // Blood. 1994. Vol. 84, N 4. P. 1020–1023.
80. Walsh K.M., Woodall T., Lamy P., et al. Successful treatment with adefovir dipivoxil in a patient with fibrosing cholestatic hepatitis and lamivudine resistant hepatitis B virus // Gut. 2001. Vol. 49, N 3. P. 436–440. doi: 10.1136/gut.49.3.436
81. Lo C.-M., Cheung S.-T., Ng I.O.-L., et al. Fibrosing cholestatic hepatitis secondary to precore/core promoter hepatitis B variant with lamivudine resistance: successful retransplantation with combination adefovir dipivoxil and hepatitis B immunoglobulin // Liver Transpl. 2004. Vol. 10, N 4. P. 557–563. doi: 10.1002/lt.20133
82. Leroy V., Dumortier J., Coilly A., et al. Efficacy of Sofosbuvir and Daclatasvir in Patients With Fibrosing Cholestatic Hepatitis C After Liver Transplantation // Clin Gastroenterol Hepatol. 2015. Vol. 13, N 11. P. 1993–2001. doi: 10.1016/j.cgh.2015.05.030
83. Forns X., Mutimer D., Manns M., et al. Ledipasvir/sofosbuvir with ribavirin for the treatment of fibrosing cholestatic hepatitis C after liver transplantation // J Hepatol. 2015. Vol. 62, Suppl. 2. P. S623–S623. doi: 10.1016/S0168-8278(15)30982-X
84. Pungpapong S., Aqel B., Leise M., et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant // Hepatology. 2015. Vol. 61, N 6. P. 1880–1886. doi: 10.1002/hep.27770
85. Merli M., Rossotti R., Travi G., et al. Sustained virological response with 16-week glecaprevir/pibrentasvir after failure to sofosbuvir/velpatasvir in post-transplant severe HCV recurrence in HIV // Transpl Infect Dis. 2019. Vol. 21, N 6. P. e13165. doi: 10.1111/tid.13165
86. Mauro E., Crespo G., Montironi C., et al. Viral eradication and fibrosis resolution in post-liver transplant cholestatic hepatitis C virus // Liver Transpl. 2018. Vol. 24, N 5. P. 703–707. doi: 10.1002/lt.25027
87. Coilly A., Sebagh M., Fougerou-Leurent C., et al. HCV eradication does not protect from fibrosis progression in patients with fibrosing cholestatic hepatitis after liver transplantation // Clinics and Research in Hepatology and Gastroenterology. 2022. Vol. 46, N 9. P. 102024. doi: 10.1016/j.clinre.2022.102024

AUTHORS' INFO

*** Vladimir E. Syutkin**, MD, Dr. Sci. (Medicine);
address: 3 Bol'shaya Sukharevskaya square, 129090 Moscow, Russia;
ORCID: 0000-0001-8391-5211;
eLibrary SPIN: 5011-6287;
e-mail: vladsyutkin@gmail.com

Vladimir P. Chulanov, MD, Dr. Sci. (Medicine), Professor;
ORCID: 0000-0001-6303-9293;
eLibrary SPIN: 2336-4545;
e-mail: Vladimir@Chulanov.ru

ОБ АВТОРАХ

*** Сюткин Владимир Евгеньевич**, д-р мед. наук;
адрес: Россия, 129090, Москва, Большая Сухаревская площадь, д. 3;
ORCID: 0000-0001-8391-5211;
eLibrary SPIN: 5011-6287;
e-mail: vladsyutkin@gmail.com

Чуланов Владимир Петрович, д-р мед. наук, профессор;
ORCID: 0000-0001-6303-9293;
eLibrary SPIN: 2336-4545;
e-mail: Vladimir@Chulanov.ru

* Corresponding author / Автор, ответственный за переписку