REVIEW

Chronic Obstructive Pulmonary Disease and Hepatitis C

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Chronic obstructive pulmonary disease (COPD) is a preventable, treatable disease with significant extrapulmonary manifestations that could affect negatively its course in some patients. Hepatitis C virus infection (HCV), on the other hand, is associated with a number of extrahepatic manifestations. COPD patients have increased prevalence of HCV and patients with HCV, especially older ones, have increased prevalence and faster progression of COPD. HCV infection exerts long-term effects on lung tissue and is an additional risk factor for the development of COPD. The presence of HCV is associated with an accelerated loss of lung function in COPD patients, especially in current smokers. COPD could represent extrahepatic manifestation associated with HCV infection. The aim of this article was to review the literature on prevalence of HCV in COPD and vice versa, pathogenetic link and the consequences of their mutual existence.

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable, treatable disease with significant extrapulmonary manifestations that could worsen the course of the disease in some patients.[1] An epidemiological study shows a prevalence of COPD in Bulgaria of 11.2% (23.7% in current smokers, 21% in former smokers, 6.6% in non-smokers)[2], which is similar to the global COPD prevalence of 11.7% among people aged >30 years[3].

The prevalence of hepatitis C in Bulgaria is 1.5%[4], whereas worldwide prevalence is 2.8%[5]. Hepatitis C virus is a small single stranded RNA virus of the *Flaviviridae* family, which is a major cause of liver cirrhosis and hepatocellular carcinoma worldwide.[6]

Hepatitis C virus (HCV) infection, in turn, is connected to a large number of extrahepatic manifestations such as mixed cryoglobulinemia, lichen planus, porphyria cutanea tarda, B-cell non-Hodgkin's lymphoma, monoclonal gammopathy, etc.[7] An increasing body of evidence supports the possibility of pulmonary involvement as extrahepatic manifestations of chronic HCV infection.[8,9]

AIM

The aim of this article was to review literature on the prevalence of HCV in COPD and vice versa, the pathogenetic link and the consequences of their mutual existence.

HCV IN COPD

The available studies on the prevalence of HCV in COPD are scant and have small sample sizes.

Erol et al. reported a prevalence of HCV infection of 8.3% in patients with COPD (n=108).[10] Forty-four point four percent of patients with HCV and COPD had risk factors for viral infection (such as blood transfusions, surgery, hemodialysis, exposure to blood or biofluids, risky sexual behavior, use of intravenous drugs, dental treatments, tattoos), while in the control group with no HCV, risk factors were found in 12.1% of patients. The two groups were matched in age, gender, smoking status and number of previous hospitalizations.

The incidence of HCV in 187 patients with COPD, according to another study, was 7.5% (95%CI

6.5-8.5), while in blood donors - 0.41% (95%CI 0.40-0.42). Patients with HCV have lower FEV_1 (34.7%) and a higher BODE index [B - body mass index, O – obstruction, D – dyspnoea, E - exercise (exercise test)] (median=6) compared to patients without HCV infection (mean FEV_1 42.7%, BODE median=4, p=0.011 and 0.027, respectively).[11]

As suggested in one of the hypotheses, chronic HCV infection leads to inflammations in the lung and is associated with development of COPD.[8]

The presence of HCV is associated with an accelerated loss of lung function in current smokers (ΔFEV_1 79.5 ml/year and $\Delta DLCO$ 4.5%/year) compared to former smokers with HCV (ΔFEV_1 54.0 ml/year and $\Delta DLCO$ 3.36%/year) and current smokers without HCV infection (ΔFEV_1 59.7 ml/year and $\Delta DLCO$ 3.50%/year), but the biggest difference is found in former smokers without HCV infection (ΔFEV_1 33.5 ml/year and $\Delta DLCO$ 2.66%/year).[8] The response to interferon treatment (negative HCV RNA) was associated with slowing in the annual decline of FEV_1 over a period of three years (from 68.4 ml/year to 57.3 ml/year) compared to patients with no response (from 65.5 ml/year to 66.1 ml/year).

The presence of HCV is also associated with worse lung function in another study - FEV_1 67 vs. 55%.[12] Lung function in this study showed correlation with the severity of liver damage according to Child (mean FEV_1 61% in Child A, 51% - Child B, 51% - Child C). However, there is no difference in the degree of obstruction (FEV_1/FVC) among patients with Child A, B and C, probably due to the decrease in FVC (presence of ascites, which hinders the movement of the diaphragm).[13]

COPD IN HCV

Studies on the prevalence of COPD in patients with HCV are also scant.

In patients with chronic HCV infection, prevalence of COPD (17.6%) and bronchial asthma (14.7%) is significantly higher compared to that in patients with hepatitis B infection matched in age, gender and smoking status (COPD 5%, bronchial asthma 1.7%).[10]

This prevalence is considerably higher in comparison with the representative study in the general population - 10.6% (15.4% male, 6% in women older than 40 years).[14] COPD patients were significantly older (60.9 vs. 46.5 years) in comparison with other characteristics. Another study found prevalence of COPD of 11.4% in patients with HCV as compared to 9.2% in patients with no HCV (n=126971, p<0.001).[15] Minakata et al. reported prevalence of COPD of 19.3% (6/31) in patients with HCV.[16]

A small study found impairment in lung function in 75% of patients with HCV (15/20). Patients with reduced FEV_1/FVC<80% ratio, suspected for COPD are 55% (11/20).[17]

However, the relative risk for COPD in HCV patients, as reported in another study, is not increased, although there is clearly a tendency for this (OR 1.69, 95%CI 0.97-2.96, p=0.066).[18] The prevalence of COPD in the same study is 14.1% (22/156).

In contrast to these results, another retrospective study found no increase in the prevalence of virus infection (hepatitis viruses A, B, and C) in patients with COPD compared to that in the control group. This low prevalence in the light of the previous studies (0.44% vs. 0.50%) could be attributed to underdiagnosis.[19]

Risk factors for COPD include smoking, occupational hazards, exposure to the environment and others, including latent viral infections.[9] Patients with HCV infection do not have increased prevalence of risk factors for COPD, despite the presence of COPD (25% vs. 33.9%, p=0.7).[10]

Interestingly, there is one study that found no increase in the prevalence of obstructive lung diseases (OLD) in HCV.[20] The authors suggested that increased prevalence of OLD (defined as prebronchodilator FEV_1/FVC <70%) may have been confounded by the strong relationship between HCV and heavy tobacco exposure. However, in this study, post-bronchodilator spirometry was not performed and the distinction between reversible (asthma) and irreversible (COPD) airflow obstruction could not be made. Moreover, smoking is a well-established risk factor for OLD, yet in this study there was no significant association between pack-years and OLD (particularly COPD) which makes the diagnosis of asthma more likely. Lastly, the low mean age (48 years) in this group also suggests significant prevalence of asthma with inability to judge the prevalence of COPD alone.

COMMON PATHOGENESIS

The exact mechanism of interaction between HCV and COPD is unclear (**Fig. 1**).

Systemic inflammation in HCV could facilitate the occurrence of COPD. COPD is characterized by increased levels of inflammatory cytokines (IL-1β, IL-6, IL-8, and TNFα) which can increase further in exacerbation.[21] There is also neutrophilic inflammation with increased local levels of IL-8, as well
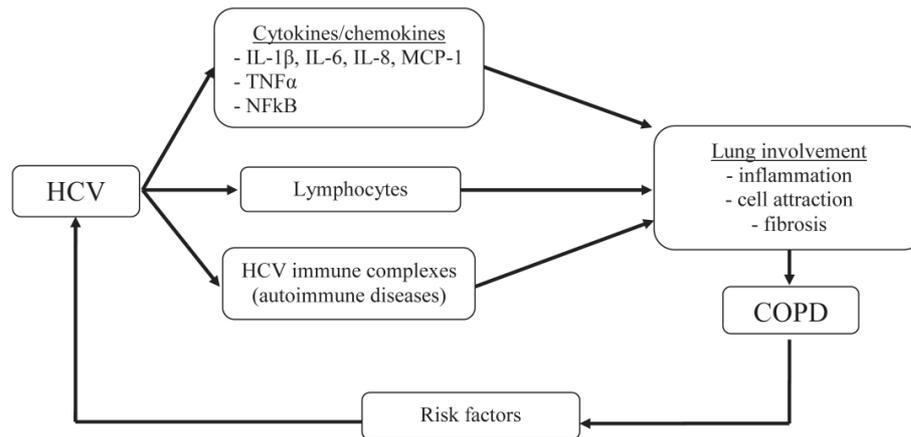
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Figure 1. Association between HCV and COPD

as NF-kB and 15-lipoxygenase.[22] In addition, the bronchial epithelium in COPD expressed an increased amount of monocyte chemoattractant protein-1 and IL-8, which is a leukocyte attractant and contribute to increased levels of neutrophils in the sputum.[23]

At molecular level, the most likely link is IL-8, which is crucial in the pathogenesis of COPD. HCV increases the level of IL-8 in endothelial cells by transcriptional activation and stabilization of the mRNA[24] and the level of IL-8 in turn is correlated with the replication of HCV[25]. In addition, HCV nuclear nucleocapsid protein increases IL-8 by p-38 and gC1qR (receptor protein, which is involved in the complement system - C1).[26]

IL-8 has a chemotactic effect on inflammatory cells such as neutrophils through CXCR receptors 1 and 2, which increases pulmonary inflammation.[27] It could directly induce bronchoconstriction and contribute to bronchial hyperresponsiveness, as well as indirectly through stimulation of neutrophil attraction and activation.[28] Serum and intrahepatic cytokines, in particular IL-8 in patients with HCV, are increased.[29,30] The expression of IL-8 can inhibit the antiviral activity of IFNγ and correlates with the degree of liver fibrosis and portal inflammation in HCV.[31,32]

The number of lymphocytes in bronchoalveolar lavage (BAL) in patients with HCV is increased, which implies involvement of HCV infection in the development of lymphocytic alveolitis.[33] Thus HCV may contribute to the development of lung parenchymal destruction. Except for increased numbers of lymphocytes, other studies showed an increased number of lymphocytes and neutrophils[34] as well as increased neutrophils only[35] in the BAL of patients with HCV. An increased number of CD2+, CD3+, CD4+ and HLA-DR+ T-lymphocytes has

also been reported.[33,34] However, these results are based on small sample sizes and in asymptomatic patients with no clinical and radiological data of pulmonary disease.

Cytotoxic CD8+ T-lymphocytes increase in viral infection and activate a series of inflammatory pathways which results in release of inflammatory mediators.[36] CD8+ cells are also involved in pulmonary inflammation in COPD as their number is increased and correlates inversely with lung function.[37]

CD8+ T lymphocytes contribute to dysregulation of M_2 muscarinic receptors whose main function is to inhibit the release of acetylcholine and prevent bronchoconstriction.[38] CD8+ lymphocytes increase the level of IFNγ, which reduces the expression of M_2-receptors in the parasympathetic neurons in the airways and increases bronchial hyperresponsiveness.[38,39]

Last, but not least, smoking-related diseases such as COPD are of great concern in the HIV-infected population which is commonly associated with HCV. The prevalence of COPD is higher in patients with HIV when compared to the general population.[40] HAART therapy has led to changes in HIV-related pulmonary diseases which prolong survival. COPD is emerging as a new source of morbidity and mortality in HIV-infected patients.[41,42]

SECONDARY INVOLVEMENT OF THE LUNG IN HCV

Secondary involvement of the lung in HCV is associated on one hand with the development of liver cirrhosis and portal hypertension and on the other - with the development of autoimmune diseases which are prevalent in patients with HCV.[7] Formation of immune complexes in the pulmonary

vasculature may represent another mechanism of lung involvement (**Fig. 1**). Chronic liver disease may lead to lung injury because of changes in liver metabolism due to circulating inflammatory mediators and/or changes in blood flow due to pulmonary hypertension.

Liver cirrhosis (due to HCV) could lead to hepatopulmonary syndrome (vasodilation) and portopulmonary hypertension (vasoconstriction).

Hepatopulmonary syndrome (HPS) is represented by the triad of liver disease (liver dysfunction), pulmonary vasodilation and impaired arterial oxygenation (hypoxemia).[43] The prevalence of HPS in patients with chronic liver disease is 10-15%.[44] The clinical presentation varies from asymptomatic course to shortness of breath, cyanosis and finger clubbing.[44] Platypnea (dyspnoea occurring when getting up from a lying position) and orthodeoxia (lowering of $PaO_2 >3$ mm Hg when getting up from a lying position) are common in patients with HPS due to pulmonary vasodilation, mainly in the lower lung lobes due to gravity.[45]

Pulmonary vasodilation is a major cause of hypoxemia in HPS. It leads to a mismatch between ventilation and perfusion due to increased perfusion and unchanged ventilation, which makes impossible the diffusion of the oxygen from the alveolar space to the center of abnormally dilated capillaries and oxygenation of hemoglobin.[45] In addition, hypoxic vasoconstriction in patients with chronic liver disease and increased pulmonary blood flow also contributes to the mismatch between ventilation and perfusion.[46]

Portopulmonary hypertension (PPH) is characterized by the tetrad: increased pulmonary pressure (>25 mm Hg at rest), increased pulmonary vascular resistance (>240 $dyn.s.cm^{-5}$), normal wedge pressure (<15 mmHg) and portal hypertension (>10 mm Hg).[47]

In most patients with PPH, portal hypertension is preceding 4-7 years on average.[48] The pathogenesis of the structural changes is not entirely clear, but include pulmonary vasoconstriction, remodeling of the muscle layer on the wall of pulmonary arteries and in situ microthrombosis and/or thromboembolic lesions.[46] Although pathological changes are similar to those shown in primary pulmonary hypertension, PPH is characterized by increased cardiac output.[49] It is notable that HIV-HCV co-infected patients have higher prevalence of PAH, which could worsen the prognosis.[50]

Last but not least, HCV infection leads to chronic liver inflammation and liver fibrosis. It is possible that HCV plays a similar role in the lung and is involved in the pathogenesis of pulmonary fibrosis.[51]

PULMONARY COMPLICATIONS OF INTERFERON THERAPY

Interferon (IFN) therapy shows good results in HCV.[52] This discovery was followed by reports of IFN-associated pulmonary complications. Most of them are reporting of cases, which impedes determination of the prevalence. They include interstitial pneumonitis, ARDS, sarcoidosis, pulmonary hypertension and pleural effusions.[53-56] According to two large studies the frequency of IFN-associated interstitial pneumonitis is 0.2-0.3%.[57,58]

Pulmonary complications of HCV therapy without IFN are still under study.

CONCLUSION

COPD patients have increased prevalence of HCV and patients with HCV, especially older ones, have increased prevalence of COPD. COPD patients have an increased risk of acquiring HCV infection due to the chronic nature of the disease and frequent medical treatment as well as presence of classical risk factors for HCV. However, patients with HCV infection don't have increased prevalence of risk factors for COPD, despite the presence of COPD.

HCV infection has long-term effects on lung tissue and is an additional risk factor for the development of COPD. The presence of HCV is associated with an accelerated loss of lung function in COPD patients, especially in current smokers. COPD could represent extrahepatic manifestation, associated with HCV infection. The most likely pathogenetic link between both diseases is systemic inflammation.

Secondary involvement of the lung in HCV is associated on the one hand with the development of liver cirrhosis and portal hypertension, and on the other - with the development of autoimmune diseases which are prevalent in patients with HCV. Liver cirrhosis can cause hepatopulmonary syndrome and portopulmonary hypertension, which further worsen the prognosis of patients with HCV and COPD.

Interstitial pneumonitis is a well-described complication of therapy with IFN, but the association with other reported complications is questionable.

CONFLICT OF INTEREST

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Хроническая обструктивная болезнь лёгких и гепатит С

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Хроническая обструктивная болезнь лёгких (ХОБЛ) является предотвратимой, лечимой болезнью со значительными внелёгочными проявлениями, которые могут оказать отрицательное воздействие на протекание заболевания у некоторых пациентов. С другой стороны, инфицирование вирусом гепатита С (HCV) связано с рядом внепечёночных проявлений, связанных с HCV инфицированием. У пациентов с ХОБЛ проявляется HCV, а у пациентов с HCV, особенно у пожилых, проявляется распространение и скоротечное развитие ХОБЛ. HCV инфицирование оказывает долгосрочное воздействие на лёгочную ткань и является дополнительным фактором риска развития ХОБЛ. Наличие HCV связано с ускоренной потерей лёгочной функции у пациентов с ХОБЛ, особенно у активных курящих. ХОБЛ может привести к внепечёночным проявлениям, связанным с HCV инфицированием. Целью данной статьи является дополнительный обзор литературы, связанной с распространением HCV и ХОБЛ, и с другой стороны, установление их патогенной связи и последствий их взаимного проявления.