REVIEW ARTICLE

Respiratory system involvement in chronic liver diseases

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KEY WORDS

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ABSTRACT

Liver diseases are often associated with respiratory complications. They may manifest as pleural effusion, interstitial lung disease, as well as various combinations of symptoms affecting the pulmonary vasculature. The duration and severity of liver disease is not always reflected by the degree of lung function impairment. On the other hand, progressive damage to the lungs significantly worsens prognosis in the course of severe liver disease. The diagnosis is difficult and often requires multidisciplinary cooperation. The effects of pharmacological treatment are not always satisfactory. In numerous cases, liver transplantation proves to be the best option.

Introduction At first glance, the lungs and liver seem to be markedly divided because they are located in two different body cavities separated by the diaphragm. However, it is known that an ongoing disease in one organ is often related to that in the other. Numerous cases of inflammatory and infectious diseases as well as tumors affecting both the lungs and liver at the same time have been reported. Moreover, some diseases such as sarcoidosis, cystic fibrosis, α1 antitrypsin (A1AT) deficiency, or cancer (e.g., carcinoid) are known to have liver and lung manifestations. On the one hand, hepatic dysfunction may affect respiratory function and, on the other, lung disorders may exacerbate liver failure through hepatocyte hypoxia. The aim of this review was to describe pulmonary symptoms secondary to hepatic lesions.

Pleural effusion (hepatic hydrothorax) Pleural effusion occurs in approximately 6% to 10% of the patients with advanced liver cirrhosis in the absence of independent pulmonary or cardiac pathology.[1] The majority of effusions (65%–85%) are right-sided, 15% are left-sided, and from 15% to 30% are bilateral.[1-3] Fluid accumulates in the lungs, as it does in other organs in the course of cirrhosis. An increase in venous pressure and in the amount of extracellular fluid associated with sodium retention at reduced oncotic pressure (associated with hypoalbuminemia) favors the formation of transudate in the pleural cavity. In most cases, pleural fluid in liver cirrhosis is associated with the presence of ascites. Microholes, so called Lieberman's pores, and the presence of negative pressure in the pleural cavity promote fluid movement to the pleural space. The symptoms are nonspecific and their intensity correlates with the amount and dynamics of fluid accumulation. The most common symptoms include shortness of breath, cough, and chest discomfort. Laboratory test results may reveal hypoxemia. The presence of fluid can be confirmed by imaging tests (X-ray and ultrasound imaging). The diagnosis is established if transudate is confirmed and other causes of fluid presence are excluded. As treatment, a reduction of sodium intake, use of diuretics, puncture of pleural cavity, or corrective surgical treatment of the diaphragm are considered. However, improved liver function has the greatest impact on the patient's condition.

Alpha-1 antitrypsin deficiency A1AT, a potent inhibitor of neutrophil elastase, is synthesized and secreted mainly by the liver. A1AT deficiency is common (one of the most common hereditary diseases in the Caucasian population) but underrecognized. It affects approximately 1 in 3000 to 5000 people. Certain types of the *A1AT* gene mutation may lead to reduced secretion and accumulation of A1AT in hepatocytes. A1AT deficiency predisposes to chronic obstructive pulmonary disease with bronchiectasis, early emphysema,

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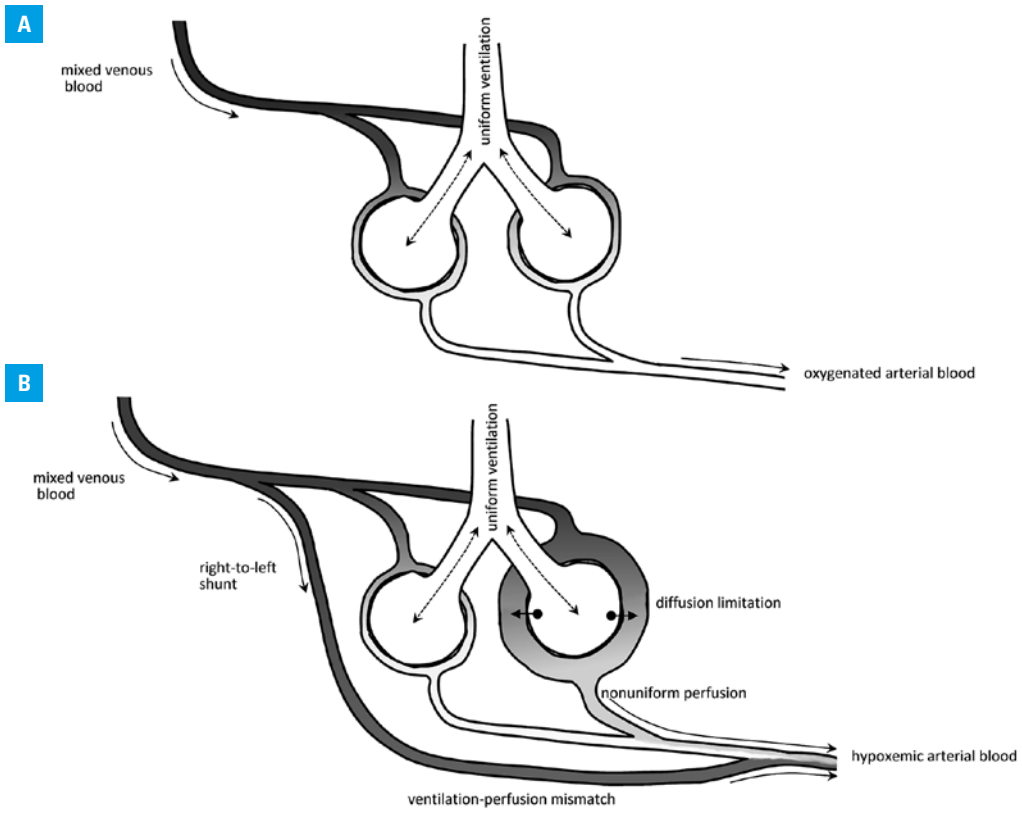

FIGURE The mechanism of formation of arterial hypoxemia in hepatopulmonary syndrome (HPS) in a two-compartment model of pulmonary gas exchange. **A** – uniformly ventilated and perfused lungs of a healthy person, with normal pulmonary capillary diameter of 8 to 15 µm, unaffected diffusion, and correct V/Q ratio. **B** – areas with enhanced pulmonary vasculature: capillaries of uneven (excessive) flow disrupt the V/Q ratio (HPS type I). Intrapulmonary right-to-left shunt, impaired diffusion of gas into the central blood flow in extended capillaries. Below right-to-left shunt by abnormal arteriovenous anastomoses (HPS type II)

and, more rarely, to liver diseases including neonatal jaundice, cirrhosis in adults, and hepatocellular carcinoma.[4] The most serious symptoms from the lungs and liver are observed in homozygous patients with P1ZZ phenotype. About 15% of the children with this phenotype can develop full-blown cirrhosis.[5] In contrast to typical emphysema, lesions are particularly pronounced in the lower parts of the lungs, which is attributed to the effect of gravitation-induced distribution of blood in the pulmonary vasculature. Shortness of breath is a typical symptom, which may manifest itself in the fourth or fifth decade of life (although 20% of homozygotes never present with symptoms of emphysema). Some patients with A1AT deficiency may develop so called hepatopulmonary syndrome (HPS). The prognosis is generally worse among smokers and translates into shorter life expectancy (even by 15 to 20 years) as compared with nonsmokers.[6]

Hepatopulmonary syndrome HPS is defined as impairment of arterial oxygenation due to pulmonary vasodilation resulting from liver disease.[7] It affects approximately 20% (range, 4%–32%) of the patients with advanced liver disease.[8] HPS is usually associated with liver cirrhosis or chronic active inflammation, but it is also observed in individuals with less common diseases such as A1AT deficiency, Budd–Chiari syndrome, as well as acute diseases leading to portal hypertension.[7,9]

HPS is caused by microscopic intrapulmonary arteriovenous dilatations observed in patients with chronic or acute liver failure. It usually has a functional character associated with dilatation of the pulmonary pre- and postcapillary vessels, which results in faster flow of systemic venous blood into the pulmonary veins partially bypassing the alveolar vasculature. This leads to hyperkinetic circulation, during which the contact of erythrocytes with the ventilated areas is shorter, resulting in an imbalance of the ventilation-to-perfusion (V/Q) ratio. A less frequent cause of the leak is related to abnormal vascular connections formed within the lung or pleura (arteriovenous anastomoses between the arterial and venous pulmonary vasculature), which increases the intrapulmonary shunt (FIGURE) as well as wall thickness of the capillaries and small veins.[10] The detailed mechanism of this phenomenon is unknown but it is thought to be caused by increased hepatic production or decreased hepatic clearance of vasodilators.

There are two anatomical types of HPS: type I, dominated by a generalized extension of the capillaries, which accelerates blood flow through the pulmonary vasculature, consequently resulting in insufficient oxygenation, and type II, in which the predominant arteriovenous connections cause displacement of the nonoxygenated blood directly to the pulmonary veins, bypassing the alveolar space.[7] For this reason, administration of 100% oxygen for breathing improves arterial oxygen saturation in the majority of patients with type I HPS, while it does not produce such a response in patients with type II HPS.[7] Furthermore, in both types of HPS, pulmonary vessels are characterized by impaired response or no response to stimuli that normally cause contraction, such as hypoxia (Euler–Liljestrand reflex). This is probably caused by increased production and impaired hepatic uptake of the factors causing

TABLE 1 Vasoactive factors that may affect the pathogenesis of hepatopulmonary syndrome

Vasodilators	Vasoconstrictors
nitric oxide	endothelin 1
carbon monoxide	endothelin 3
prostacyclin	serotonin
prostaglandins 1 and 2	tyrosine
vasoactive intestinal peptide	noradrenalin
calcitonin	angiotensin II
glucagon	vasopressin
atrial natriuretic peptide	
brain natriuretic peptide	
platelet derived growth factor	
ferritin	
estrogens	

vasodilation, which enter the pulmonary circulation in excessive amounts. These substances include, among others, prostacyclin, prostaglandin E1, vasoactive intestinal peptide, calcitonin, and glucagon. In addition, in the course of cirrhosis and portal hypertension, atrial natriuretic factor, nitric oxide (NO), platelet activating factor, growth factors, and endothelium-derived liver factor are activated.[11] NO acts as an endothelium-derived relaxing factor, causes the relaxation of vascular myocytes, and inhibits the production of strong vasoconstrictors (endothelin 1 and 3). Moreover, it stimulates the activity of hemooxygenase, which enhances the synthesis of CO and, thereby, the effect of vasodilators.[12] Increased NO production seems to be one of the most important factors leading to the extension of pulmonary bearings, but the exact relationship between the production of NO and HPS has not been fully elucidated.

It has been proved that the NO concentration in exhaled air in patients with HPS is significantly higher than that in healthy individuals and returns to normal after liver transplantation, when HPS symptoms are resolved or significantly reduced.[7,13] Schenk et al.[14] have shown the inhibitory effect of methylene blue on the effects of NO (in vascular smooth muscle cells) and, as a consequence, an improvement in oxygenation. HPS involves an imbalance between factors with vasodilatory and vasoconstrictory effects (**TABLE 1**). Experimental studies confirmed the effect of endothelin 1 and tumor necrosis factor (TNF) on the development of HPS in a rat model. Pentoxifylline, which is an inhibitor of TNF production in macrophages, prevents the development of HPS in these animals.[15]

HPS symptoms in patients with liver disease are nonspecific. Generally, they start with exercise dyspnea followed by dyspnea at rest with possible cyanosis and clubbed fingers.[16] Shortness of breath is another nonspecific symptom and the most common reason for seeking medical advice also in patients with chronic obstructive pulmonary disease, which results from cigarette smoking, a frequent habit in patients with alcoholic cirrhosis.[17] Telangiectasia (also called vascular spiders) in the skin or mucous membranes or both can be frequently observed. The presence of platypnea (increased dyspnea when changing position from reclining to standing or sitting) and orthodeoxia (deterioration of gas exchange with a decrease of partial pressure of oxygen in arterial blood [PaO_2] ≥5% or ≥4 mmHg in an upright position) are considered to be characteristic signs of this syndrome.[6] In the upright position, blood flow in vessels of the lower lung lobes (where the above vascular changes are mostly observed) is increased, which enhances nonoxygenated blood leakage and lowers PaO_2. It is believed that one of the mechanisms causing this phenomenon is the lack of the vasoconstriction reflex, which, in normal conditions, is responsible for local adaptation of the V/Q ratio. Orthodeoxia occurs in 88% of the patients with HPS, but it is not pathognomonic for HPS and can be found in patients with other chronic lung and cardiovascular diseases (e.g., atrial septum defect).[18]

The diagnosis of HPS is based on the presence of 3 criteria (**TABLE 2**). The first criterion is the documented presence of advanced liver disease (usually cirrhosis). The second criterion involves abnormalities of gas exchange. An increased alveolar-capillary gradient for oxygen pressure, $P(A\text{-}a)O_2$, is a more sensitive indicator of oxygenation disturbances than a decrease in PaO_2. Therefore, the diagnostic criteria for gas exchange abnormalities in HPS include an increased $P(A\text{-}a)O_2$ ≥15 mmHg (20 mmHg in patients above 64 years of age) with or without concomitant arterial hypoxemia (arterial PO_2 <80 mmHg). The alveolar-arterial gradient can be calculated using the following formula:

$$P(A\text{–}a)O_2 = \frac{[P_{atm} - 47 - (PaCO_2 + PaO_2)]}{FiO_2}$$

where P_{atm} stands for atmospheric pressure; $PaCO_2$ for partial pressure of carbon dioxide in arterial blood; PaO_2 for partial pressure of oxygen in arterial blood; and FiO_2 for the fraction (percentage) of oxygen in the inspired air.

The presence of reduced diffusion capacity for carbon monoxide (DL_{CO}) may facilitate diagnosis because it is observed in most interstitial lung diseases as a result of the imbalance in the V/Q ratio. However, it is a nonspecific symptom and it can persist (as opposed to other indicators of gas exchange) even after liver transplantation, suggesting a permanent reconstruction (remodeling) of the pulmonary vessels.[16]

The third criterion required for the diagnosis of HPS is the evidence of abnormal generalized or local pulmonary vasodilation (intrapulmonary vascular dilatation).[7] Contrast echocardiography with bubble air is a sensitive, noninvasive, but solely qualitative, method to identify pulmonary vasodilation. Abnormal pulmonary vasodilation is indicated by the presence of contrast (air

TABLE 2 Diagnostic criteria for hepatopulmonary syndrome

	Criterion	Conditions for HPS positive
1	clinical (liver disease)	documented chronic liver disease with portal hypertension (most common) with or without cirrhosis
2	blood gases (oxygenation defect)	$P(A–a)O_2$ ≥15 mmHg[a] or PaO_2 <80 mmHg (ambient air breathing)
3	confirmation of intrapulmonary vascular dilatation	positive contrast-enhanced echocardiography (with bubble air) or extrapulmonary (brain uptake of radioisotope after 99m TcMAA lung scanning >6%)

a for individuals over 64 years of age: 20 mmHg[7]

Abbreviations: $P(A-a)O_2$ – alveolar-capillary gradient for oxygen pressure (normal range, 4–8 mmHg), PaO_2 – oxygen pressure in arterial blood (normal range, 80–100 mmHg), TcMAA – ^{99}Tc isotope-labeled albumin macroaggregates (approximately 20 μm in diameter)

TABLE 3 Severity of hepatopulmonary syndrome

Severity	$P(A-a)O_2$, mmHg	PaO_2, mmHg
mild	≥15	≥80
moderate	≥15	≥60 to <80
severe	≥15	≥50 to <60
very severe	≥15	<50 (<300 when breathing 100% O_2)

Borderline values for patients aged 64 years and older: $P(A–a)O_2$ ≥20 mmHg; PaO_2 <70 mmHg

Abbreviations: see TABLE 2

bubbles form an isotonic sodium chloride solution given into a peripheral vein) in the left atrium of the heart. Physiologically, after leaving the right ventricle, the bubbles are trapped in the pulmonary circulation, where the capillary diameter (8 to 15 μm) is too small to let them pass through, whereas in HPS, in which the vessels are dilated up to 50 μm and higher, contrast occurs in the left atrium after 3 to 6 cycles of the heart, confirming the presence of intrapulmonary leaks. This test is considered to be the gold standard in the diagnosis of HPS. In addition, the echocardiographic measurement of the left atrial maximum volume (≥50 ml) indicates the presence of HPS in patients with liver cirrhosis.[19] Other methods include scintigraphy, which, in the case of the arteriovenous shunts, may show 99Tc isotope-labeled albumin macroaggregates (approximately 20 μm in diameter) in the brain and kidneys (>6% of the administered dose). Pulmonary angiography is helpful in the differential diagnosis (e.g., with pulmonary embolism as a cause of dyspnea) and quantitative assessment of vasodilation, and it also enables to classify vascular changes into generalized or local.[5,7]

The relationship between the severity of liver disease and that of HPS remains controversial. However, it has been documented that the degree of gas exchange impairment affects the outcome and survival in patients with HPS.[20,21] The severity of arterial hypoxemia reflects that of HPS, although hypoxic respiratory failure alone is rarely a direct cause of death.[16] Rodrigez-Roisin et al.[7] suggested to classify the severity of disturbances in the course of HPS as mild, moderate, severe, and very severe (TABLE 3).[7]

Chest radiography in patients with HPS is nonspecific and usually shows no abnormalities; however, the lesions are predominately located in the lower lungs, which may be associated with increased vasculature.[5]

Pharmacological treatment of HPS has been ineffective so far. Studies focused on the use of methylene blue, sympathomimetic agents, aspirin, indomethacin, somatostatin analogues, and almitryne.[7,12,14] None of those agents have proved to be effective enough to be recommended for general use in HPS. First-choice nonsurgical treatment in patients with HPS and severe hypoxemia is long-term oxygen therapy. Liver transplantation seems to be the most effective treatment, especially in patients with early vascular lesions.[7,16] Only such management improves the outcome and survival and reduces symptoms associated with HPS. Therefore, it is vital to schedule patients for transplantation as soon as possible, although with an awareness that hypoxemia in the course of HPS increases the risk of postoperative complications.[20,22,23] The mortality rate during a 5-year follow-up is approximately 20%.[24]

Portopulmonary hypertension Portopulmonary hypertension (PPHTN) is a type of pulmonary arterial hypertension that occurs in patients with portal hypertension. It most often develops in patients with portal hypertensions in the course of liver cirrhosis but may also affect individuals without liver pathology as a result of so called prehepatic block.[7] PPHTN differs from other types of pulmonary hypertension associated with liver disease in terms of the presence of structural changes (remodeling) in pulmonary vessels resulting in an increase of pulmonary vascular resistance. Other types of pulmonary hypertension result from an increase in blood volume and cardiac output (hyperkinetic circulation), with normal or sometimes even reduced pulmonary vascular

TABLE 4 Diagnostic criteria for portopulmonary hypertenstion[7]

Liver disease causing portal hypertension (with or without cirrhosis)
mPAP >25 mmHg
mPAOP <15 mmHg
PVR >240 dyn·s·cm^{-5} (3.0 mmHg·l^{-1}·min^{-1})[a]

a diagnostic criterion of PVR may differ (120–240 dyn·s·cm^{-5})

Abbreviations: mPAP – mean pulmonary artery pressure, mPAOP – mean pulmonary artery occlusion pressure, PVR – pulmonary vascular resistance

resistance.[25] PPHTN affects from 3% to 5% of the patients, which makes it a much less common complication of liver disease than HPS.[26,27] The average age at diagnosis is between 50 and 60 years, with no sex predilection.[28]

The pathogenesis of PPHTN is complex and has not been fully clarified. The possible mechanisms of vascular lesions include a reaction of the epithelium to increased pulmonary blood flow, inflammatory reaction owing to an increased exposure to intestinal microbes and endotoxins, imbalance of vasoactive agents, autoimmune reactions, and the effect of genetic factors.[7,28]

Symptoms of PPHTN usually appear late and correlate with the severity of hypertension but not with that of liver disease. The most common symptoms are increasing dyspnea, chest pain, syncope, and rarely hemoptysis. A significant reduction in arterial PaO_2 and cyanosis are not usually observed.[5] A physical examination may reveal a widening of the neck veins and a murmur of tricuspid regurgitation indicating right ventricular overload. Chest radiography findings suggesting pulmonary hypertension in the form of enlarged cardiac silhouette (especially in the right ventricle) and enlargement of the main branches of the pulmonary artery, as well as electrocardiographic features of the right ventricular overload have low sensitivity and specificity, and have no major significance, especially in the early diagnosis of PPHTN. Echocardiography is a screening diagnostic tests that shows the characteristic features of pulmonary hypertension with a sensitivity of 100% and specificity not exceeding 50%. In some patients, pulmonary hypertension may be associated with hyperkinetic circulation in the course of HPS, without an increase in pulmonary vascular resistance. In this population, right heart catheterization is a reference test. It is important to differentiate between those two syndromes because in patients with PPTHN, unlike in those with HPS, liver transplantation usually does not reduce respiratory symptoms.

The diagnostic criteria in PPHTN include portal hypertension, elevated mean pulmonary artery pressure (mPAP) exceeding 25 mmHg at rest, mean pulmonary artery occlusion pressure of less than 15 mmHg, and elevated pulmonary vascular resistance above 240 dyn·s·cm^{-5} (TABLE 4).[7]

Based on the mPAP level, the severity of PPHTN is classified as: 1) mild (mPAP >25–34 mmHg); 2) moderate (mPAP, 35–44 mmHg), severe (mPAP ≥45 mmHg).

There have been no randomized clinical trials to confirm the effectiveness of any of the following therapeutic interventions: vasodilators such as prostacyclin and its analogs (epoprostenol, iloprost), endothelin receptor blocker (bosentan), or selective blocker phosphodiesterase-5 (sildenafil).[29] In patients with hypoxemia, oxygen therapy is used to reduce vasoconstriction induced by the reflex activated by a decrease in PaO_2. The effect of liver transplantation on the course of PPHTN cannot be predicted. Intra- and postoperative mortality is particularly high in patients with severe disease (60%–100% when mPAP exceeds 50 mmHg). Therefore, predominantly patients with mPAP of less than 35 mmHg are referred for surgery.[7] Recent studies have shown that the survival rate in patients with PPHTN is similar to that of patients with primary pulmonary hypertension and reaches 88% after 1 year and 75% after 3 years.[29]

Chronic autoimmune liver diseases The relationship between autoimmune liver diseases and lung lesions is not clear. It is possible that these diseases should be regarded as systemic with multiple-organ manifestations.

Primary biliary cirrhosis Primary biliary cirrhosis (PBC) is an obstructive cholestatic disease with progressive damage to the intrahepatic bile with possible lesions in the lungs. The etiology of those lesions is unknown but they may have an autoimmune origin, which leads to chronic granulomatous changes in intrahepatic ducts and, consequently, to destruction of the ducts, intrahepatic stasis, and even organ dysfunction.

The prevalence of PBC varies geographically, ranging from 40 to 400 per 1,000,000 people, mainly in middle-aged women (women-to-men ratio, 10:1). Familial occurrence is also observed.[30,31] PBC may be associated with other autoimmune diseases such as rheumatoid arthritis, Hashimoto thyroiditis, scleroderma, Sjögren's syndrome, systemic lupus erythematosus, and Crohn's disease.[32,33]

It is considered that from 50% to 60% of the patients at diagnosis did not report any symptoms, and about one third of the patients remain asymptomatic for many years of the disease. The most common symptoms are fatigue and pruritus.[30] Laboratory findings include hypergammaglobulinemia and PBC-specific antimitochondrial antibodies type II (AMA2), which may occur even years before the diagnosis. In some patients (predominantly women), elevated alkaline phosphatase (AP) activity and cholesterol levels are observed. These simple and widely available tests may suggest PBC as a cause of parenchymal infiltrations in the lungs.

The current diagnostic criteria for PBC are based on the presence of 2 of 3 conditions: 1) features of chronic (lasting more than 6 months) cholestasis with increased AP, and γ-glutamyl transpeptidase (GGTP); 2) the presence of AMA

TABLE 5 Diagnostic criteria for autoimmune hepatitis[42]

Antibodies / changes	Diagnostic level	Points
ANA lub SMA	≥1: 40	+1
ANA lub SMA	≥1: 80	+2
anti-LKM 1	≥1: 40	+2
anti-SLA	present	+2
IgG	>ULN	+1
	>1.1 ULN	+2
histological findings	compatible	+1
	typical for AHI	+2
viral infections	lack	+2

Diagnosis is confirmed when scoring ≥7 points; diagnosis is likely (probable) at scoring value of 6 points.

Abbreviations: ANA – antinuclear antibodies, anti-LKM-1 – type 1 antibody against liver-kidney microsome, anti-SLA – antibodies against soluble liver antigen, IgG – immunoglobulin class G, SMA – smooth muscle antibody, ULN – upper limit of normal

in a titer of ≥1:40 and /or AMA2 antibodies; or 3) liver biopsy histology corresponding to PBC.[34]

Usually, the diagnosis of liver disease precedes pulmonary complications, although the reverse also occurs. Changes in the respiratory system are usually manifested as interstitial lung disease (ILD), rarely as obstructive bronchitis or severe pulmonary hypertension. The incidence of ILD in patients with PBC is estimated at over 15%.[35] Among ILDs, lymphoid interstitial pneumonia, fibrosis, and organizing pneumonia are reported. Granulomas similar to those observed in sarcoidosis may also be present.[36] Occasionally, alveolar hemorrhage may be reported.[5,32]

Clinical, radiological, and functional findings in the lungs correspond to those observed in other ILDs. Symptoms are reported by half of the patients. The most common complaint is shortness of breath (>50% of the patients) and cough (>35% of the patients). A physical examination may reveal localized crackles in the lower lung fields (>35% of the patients).[37] In more than 60% of the patients, changes may be observed already on conventional chest radiography. The most common functional disorder is impaired DL_{CO}.

In a large number of patients with PBC, an increased number and percentage of lymphocytes in the bronchoalveolar lavage (BAL) fluid and increased ratio of CD_4 to CD_8 lymphocytes are observed. However, the presence of lymphocytosis in the BAL fluid is not always associated with the presence of noticeable changes in a classic chest x-ray examination.[37,38] Similarly to other chronic liver diseases, progression of hepatic lesions may lead to HPS (as discussed above), and in 12% of the patients the development of pulmonary hypertension is observed.[37]

Lung lesions in the course of PBC, as in other types of autoimmune hepatitis, often respond to treatment with corticosteroids, without effect on liver changes.[5,32] The effects of treatment with ursodeoxycholic acid on PBC are ambiguous. Liver transplantation is generally effective, although recurrences in the transplanted organ have been reported.[39]

Primary sclerosing cholangitis Primary sclerosing cholangitis (PSC) is another cholestatic liver disease of unknown etiology. The changes affect both the inside and extrahepatic bile ducts, in which an ongoing inflammatory process along with the formation of granulation tissue and fibrosis leads to progressive loss of patency and development of cholestasis. In contrast to PBC, PSC occurs twice more often in young men, and in 70% to 80% of the cases, it coincides with inflammatory bowel diseases (typically with colitis ulcerosa).[34]

Diagnosis of PSC is based on the presence of abnormalities on endoscopic retrograde cholangiopancreatography or noninvasive magnetic resonance cholangiography in patients with clinical and laboratory symptoms of cholestasis (increased AP and/or GGTP activity) after exclusion of secondary narrowing cholangitis (e.g., in the course of congenital abnormalities or AIDS, due to postoperative lesions, or after treatment with some cytostatic drugs).[34,40] Autoimmune character of the disease is confirmed by the presence of perinuclear antineutrophil cytoplasmic antibodies (present in 26%–94% of the patients), antinuclear antibodies (ANA, in 8%–77% of the patients), smooth muscle antibody (SMA, in up to 83% of the patients).[32,34]

Half of the patients report abdominal pain, itching, weight loss, and fever episodes.

Pulmonary complications, apart from ILD resembling sarcoidosis, may include interstitial fibrosis, organizing pneumonia, and alveolar hemorrhage. An association between methotrexate treatment and ILD in patients with PSC has been reported.[32] At present, there are no clear recommendations regarding the treatment of patients with PSC. Similarly to PBC, liver transplantation improves prognosis in this group of patients.[41]

Autoimmune hepatitis Autoimmune hepatitis (AIH) is the most common autoimmune disease of the liver. It has a prevalence of 10–20 per 100,000 population and mostly affects women (women-to-men ratio of 3.5:1).[42] The onset is usually slow but it leads to severe

liver damage and even to death within 6 months from diagnosis if no treatment is applied. Symptoms are nonspecific and include general weakness (fatigue), loss of appetite, joint pain, abdominal pain, and, occasionally, jaundice. In 25% of the patients, early AIH is asymptomatic. Laboratory tests may reveal elevated transaminase activity, hypergammaglobulinemia, the presence of ANA, SMA, and type 1 antibody against liver-kidney microsome. There are no specific clinical or laboratory tests, which poses an additional difficulty in the diagnosis of AIH. Numerous cases of the overlapping syndrome of AIH and PBC or PSC have been reported.[43,44]

Diagnosis is established only after exclusion of other causes of chronic liver conditions, based on an internationally adopted scoring system (**TABLE 5**).[45]

Recently published reports have changed the opinion on the frequency of interstitial lung complications in the course of AIH. Currently, it is believed that pulmonary complications in the course of AIH, such as interstitial fibrosis or changes resembling lymphoid interstitial pneumonia after exclusion of iatrogenic changes, are less prevalent than it was previously believed.[32] Beneficial effects of pharmacological treatment with prednisone alone or in combination with azathioprine have been reported.[42]

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ARTYKUŁ POGLĄDOWY

Zajęcie płuc w przebiegu przewlekłych chorób wątroby

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SŁOWA KLUCZOWE

nadciśnienie wrotno-płucne, pierwotna żółciowa marskość wątroby, pierwotne stwardniające zapalenie dróg żółciowych, płyn w opłucnej, zespół wątrobowo-płucny

STRESZCZENIE

Chorobom wątroby nierzadko towarzyszą powikłania ze strony układu oddechowego. Mogą się one manifestować jako płyn w opłucnej, zmiany o typie śródmiąższowej choroby płuc, a także złożone zespoły objawów, w tym takich, które mają wpływ na naczynia płucne. Czas trwania i zaawansowanie choroby wątroby nie zawsze przekładają się na stopień upośledzenia czynności płuc. Natomiast konsekwencje postępującego uszkodzenia układu oddechowego w istotny sposób pogarszają rokowanie w przebiegu zaawansowanych chorób wątroby. Diagnostyka zmian jest trudna i wymaga specjalistycznej wielokierunkowej współpracy. Efekty leczenia farmakologicznego nie zawsze są zadowalające. Najskuteczniejszym postępowaniem w wielu sytuacjach okazuje się przeszczepienie wątroby.

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