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CLINICAL CASE

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COMBINATION OF AUTOIMMUNE HEPATITIS WITH SYSTEMIC LUPUS ERYTHEMATOSUS. CLINICAL OBSERVATION

Abstract: The autoimmune hepatitis (AIH) is a chronic disease of the liver with different clinical phenotypes where significant roles have autoimmune processes of failed self-tolerance mechanism to own hepatocytes. Some other autoimmune diseases such as lupus are also observed with AIH. On the example of clinical observation we present features of course of the AIH with lupus on the background, the challenges of the diagnosis and treatments. During the research we identified a relationship between two autoimmune diseases based on association of autoimmune disorders with major histocompatibility complex.

Keywords: Autoimmune hepatitis, lupus, autoantibodies, liver encephalopathy, immunosuppressive therapy.

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Autoimmune hepatitis (AIH) is a chronic diffuse liver disease with various clinical phenotypes, laboratory and histological manifestations. The worldwide prevalence of AIH is increasing annually, currently at <30 cases per 100,000 people, regardless of age and ethnicity, with a gender ratio of 4:1 for women over men [7].The most important issue in the study of this disease is the search for trigger factors and genetic predisposition. In clinical practice, there are also acute problems of early diagnosis and differentiation with other diseases. Thus, most cases are observed among women with increased gamma globulin titers, Immunoglobulin G (IgG), presence of antibodies (Abs) as well as human leukocyte antigen (HLA) DR3 and DR4, morphological signs of periportal hepatitis and a favorable response to immunosuppression [6].

To date, the pathogenesis of AIH remains incompletely understood. It is known that autoimmune processes with impaired tolerance to the liver's own cells are crucial. In clinical practice, timely diagnosis of AIH is difficult, the disease may have a fulminant course, which not infrequently leads to the omission of the possibility of timely therapy in the initial stages of the disease, as well as the development of other autoimmune or immune-mediated pathological diseases. Among them, there is an association of AIH with systemic lupus erythematosus (SLE).

Autoimmune or immune-mediated diseases such as autoimmune thyroiditis, rheumatoid arthritis, type-1 diabetes, systemic lupus erythematosus, Sjögren's syndrome, celiac disease and immune thrombocytopenic purpura may develop at any stage of AIH. SLE is characterized

by a genetic abnormality of B- and T-lymphocytes, which in turn synthesize cytotoxic Abs. The resulting immune complexes containing antinuclear antibodies (ANA) stimulate Th1-induced connective tissue inflammation. According to the literature, it is known that AIH with HLA-DR4 is predominantly prevalent in Southeast Asia, Japan the clinical course of the disease is characterized by frequent systemic manifestations [1, 2, 7, 8] .

The association of AIH with SLE suggests the presence of common links in the pathogenesis of these diseases. There are insufficient data in literature on peculiarities of course and treatment of comorbid patients. The aim of our study is to study clinical case of concomitant autoimmune pathology of AIH and SLE, peculiarities of the course, diagnostics and treatment tactics of the disease.

We present a clinical case of combination of AIH with SLE in a patient residing in the Republic of Sakha (Yakutia).

Patient V., born in 1968, was hospitalized for inpatient treatment in January 2020 at the gastroenterological department of Yakutsk Republican Clinical Hospital (YRCB).

Complaints upon admission: pain, sense of gravity in the right subdermal region, jaundice of the skin, general weakness, loss of body weight, swelling of the lower extremities.

Past medical history: Patient B. had 5 pregnancies, 5 births (4 girls, 1 boy). Heredity: Mother and elder sister died of severe liver failure on the background of liver cirrhosis of unknown etiology, the rest had no pathology.

Anamnesis: Considers himself sick since 2010. when, within 2 months, an ulcer appeared in the region of the left tibia, fever, arthralgia, a symptom of a «butterfly» on the face, Le-cells were detected in the blood and the diagnosis of SLE, Raynaud syndrome were verified. Prescribed steroid therapy with prednisone 15 mg/day resulted in stable clinical remission. Until 2019 the patient had no complaints, she did not take any further steroid therapy. During the period from 2010-2019, the patient was operated for a falxmeningioma of the brain (2017), diagnosed with type-2 diabetes, insulin-independent variant (2018). In May 2019, during the check-up, the level of the cancer marker alpha-fetoprotein (AFP) increased to 48.1 IU/ml, with a subsequent increase to 159 IU/ml (Nov. 22, 2019) and 201.6 IU/ml (Jan. 20, 2020) on the background of weight loss and an increase in general weakness.

In November 2019, in order to rule out carcinogenic pathology, she was referred to the National Center of Medicine - Yakutsk City Hospital No. 1. In the course of diagnostics oncopathology was excluded. Serum cytolysis and cholestasis syndrome values were within the reference values (Table 1). In January 2020 due to increasing pain syndrome in the right subcostal area, jaundice of skin, mucous membranes and diarrhea the patient was urgently admitted to the regional hospital with suspicion of acute cholecystitis, mechanical jaundice. Further, 7 days later, given the severity of her condition and the ineffectiveness of the therapy she was urgently hospitalized by ambulance to the Emergency Medical Center - Yakutsk Hospital No. 2. Blood chemistry on January 13, 2020: total bilirubin (BIL-T) -182.1 μmol/L, direct bilirubin (D-BIL) -126 μmol/L, alanine transaminase (ALT) - 88 U/L, alkaline phosphatase (ALP) - 513 U/L, total protein (BELOK) -75.7 g/L, glugose (GLU) - 3.09 mmol/L. In the hospital, weakness and jaundice progressed. On January 15, 2020 the blood chemistry showed signs of marked cytolysis syndrome (ALT/aspartic transaminase (AST) - 417.5/1533.8 U/L), marked cholestasis (BIL-T 165.1 μmol/L, D-BIL - 149.6 μmol/L, gamma-glutamyl transpeptidase (GGT) - 77.5 U/L, ALP - 378 U/L), hepatosuppression syndrome (albumin - 20.1 g/l, Quik prothrombin - 28%, international normalized ratio (INR) 2.45). There was an increase in the dynamics of serum oncomarkers (AFP) to 201.6 IU/ml, antibodies to ds-DNA (anti-dsDNA) concentration of 118.80 IU/ml, Immunoglobulin E (IgE) concentration of 248 IU/ml, and detection of positive antinuclear antibodies (ANA). Components of the complement system C3/C4 were not detected (Table 2).

Ultrasound of the abdominal cavity organs, computed tomography with contrast revealed signs of hepatosplenomegaly, diffuse changes of the parenchyma, signs of cholelithiasis (GI). On the basis of high cytolytic serum transaminase values, a steroid therapy with Prednisolone 60 mg/day was started. During the first days against the background of this treatment, the patient's serum transaminase values decreased: ALT 195.8 U/l, AST 347.7 U/l, ALP 315.2 U/l, BIL-T to 135.2 μmol/l, D-BIL 97.8 μmol/l, C-reactive protein (CRP) 12.93 mg/l (Table 1). On the fourth day of steroid therapy, signs of progressive hepatic encephalopathy suddenly appeared, with somnolence, disorientation, left-sided hemiparesis, and sensory impairment on the left side. Infusion of Hepa-Mertz (Ornithine) 20 mg/day, purging enemas, Dufolac (Lactulose) 30 ml/day, Ursosan (Ursodexycho-

Table 1

Blood chemistry in dinamics

Serum indicators	22.11. 2019	15.01. 2020	20.01. 2020	27.01. 2020	04.02. 2020	11.02. 2020	03.03. 2020	21.04. 2020	29.06. 2020	17.08 2020	05.10. 2020
GGT, units/L		77.5	54.0	53.0	52.0	58.0		32.0	37		
BIL-T, μmol/L	15.0	182.1	201.0	161.0	117.0	136.0	113.6	68.0	29.5	28.1	16.9
D-BIL, μmol/L		149.6	169.6	136.1	99.5	115.9	91.9	53.9	21.1	8.4	3.5
ALT, U/L	9.0	417	299.1	173.9	181.5	178.4	117.2	37.8	24.7	39	53
AST, U/L		1533.8	981.4	397.4	455	436.4	341	66.4	76.9		
Urea, mmol/L		2.6	2.8	3.6	3.6	3.8	4.2	4.8		5.62	5.62
Albumin, g/L		20.1	29	38	36	36	26.8	30	29.8		
Creatinine, mmol/L	93	54	78.0	83.0	77.0	84.0	77	78.0		74.5	83
Cholesterol, mmol/L		3.6	2.9	4.6	4.1	3.9	2.36	3.0	4.2	3.66	5.1
ALP, U/L		378	293	275	255	272		196		765	
CRP, mg/l			9.8	14.8	14.8	11.4		20.4			
BELOK, g/L		75.6	75.1	84.4	81.5	84.4		72.0	69.4	64.5	73
Glucose, mmol/L	4.0	4.30	4.45	3.85	7.93	4.53	4.04	4.25	6.34	5.01	5.51

lic acid) 750 mg/day were performed. For correction of blood coagulopathy-Dicinon 4 ml and Vikasol 10 mg/ml. The patient's condition slightly improved against the background of the therapy, but her general weakness, rapid fatigability, and weakness in the left extremities persisted. Subsequently, according to the decision of the medical council, it was decided to refrain from the prescription of targeted therapy and continuation of maintenance dosage of steroids due to the high risk of re-progression of hepatic encephalopathy. In mid-February 2020, she was discharged in stable condition with the diagnosis: Mixed etiology liver cirrhosis, Child-Pugh class B, decompensated. SLE, chronic course. Raynaud's syndrome. In April 2020, the patient again progressed symptoms of hepatic encephalopathy, against the background of reappointed therapy with Prednisolone 90 mg/day, for which the treatment with Ornithine and Ursodeoxycholic acid was cancelled and prescribed. The differential diagnosis was made in March 2020 with the purpose of immunological analysis of the blood markers of AIH: IgG-30.67 g/l; ANA - positive; determination of the antibody titers to smooth muscles class (S-SMA) IgG, IgA, IgM 1:160; Abs to microsomal fraction of the liver and kidneys (anti-LRM) <1:40. The diagnosis of AIH 1 type was confirmed (Table 3).

Taking into account clinical and anamnestic, laboratory results, the patient was clinically diagnosed:

Primary: Autoimmune hepatitis type 1, high degree of activity. Liver cirrhosis of mixed genesis, grade B according to Child-Pugh, decompensated.

Complications: Portal hypertension, varicose esophageal veins, coagulopathy. Chronic hepatic insufficiency. Hepatic encephalopathy type C, class II, recurrent, provoked (stool retention).

Concomitant: Systemic lupus erythematosus, chronic course, activity 1, test ANA, anti-dsDNA positive. Type-2 diabetes, subcompensated. GIBS. Chronic calculous cholecystitis in remission. Condition after bifrontal bone-plastic craniotomy microsurgical removal of falxmeningioma dated May 15, 2017.

Against the background of ongoing therapy, there is a decrease in cytolysis syndrome indices from 29.06.2020. (ALT/AST - 24,7/76,9 U/L), cholestasis (total bilirubin - 29,5, direct - 21,1 μmol/l, GGT - 37 U/L) (Table 1). In dynamics there was some increase of transaminases and ALP in blood.

Based on the above history, clinical picture of the disease course, the diagnosis of SLE in this patient B. was made before AIH verification. It can be assumed that these diseases are characterized by common links of pathogenesis. Thus, there is an association of autoimmune disorders with human major histocompatibility complex. It is known that most autoimmune diseases, particularly SLE and AIH, are associated with the presence of the following antigens in the HLA phenotype: DRB1, DR2 and DR3, DR4, respectively [2, 3]. Presumably, the genes of the HLA system are involved in T-lymphocyte selection, a process that is impaired in the presence of certain alleles, resulting in the failure to eliminate sensitized T-lymphocytes to autoantigens. This relationship has significance in the diagnosis of AIH: the presence of a history of SLE indicates impaired immune tolerance associated with the HLA-complex.

Table 2

Иммунологические маркеры крови СКВ от 19.12.2019 г.

Показатель крови	Результат	Референсное значение
Антитела IgG к двуспиральной (нативной) ДНК (анти-dsDHA), МЕ/мл	118,80	< 10
Иммуноглобулин Е (IgE) (total), МЕ/мл	248	0–100
С3 компонент комплемента, г/л	0,86	0,9–1,8
С4 компонент комплемента, г/л	0,13	0,1-0,4
Антинуклеарные антитела, IgG (АНА)	Положительно	Отрицательно

According to the literature, often one of the variants of the onset of AIH is observed by the manifestation of extrahepatic manifestations, fever, arthralgia for several years and can be mistakenly regarded as SLE, rheumatoid arthritis [1, 3, 7, 8]. The course of AIH in association with SLE is characterized by the following features: manifestation of clinical manifestations of AIH with a sharp increase in laboratory indices occurs in a shorter period of time. In our clinical observation it was 8 months. During this period, the patient had pronounced clinical symptomatology of hepatic encephalopathy, which developed lightning fast against the background of glucocorticosteroid treatment. According to literature data, in most cases of AIH without treatment, cirrhosis develops within three years, and the prognosis is more serious than in patients with chronic viral hepatitis [3, 4, 5]. In this patient with pathogenetic therapy, cirrhosis developed within less than 1 year. It could be related to variability of disease course connected with peculiarities of antigenic histocompatibility, with the role of transcription factor designated as autoimmune regulator of type 1, which causes predisposition to AIH development.

Conclusion: The present clinical observation shows the course of AIH against the background of SLE, which is characterized by rapid progression with the outcome in liver cirrhosis, early manifestation of clinical symptomatology, as well as a pronounced manifestation of hepatic encephalopathy. For final verification of AIH type 1, liver biopsy with detection of characteristic morphological picture of AIH - lobular hepatitis with bridging or massive necroses, emperipolysis, hepatocytic rosettes - is required.

If a patient has signs of liver damage with impaired immune system tolerance, it is recommended to rule out AIH at an early stage. In the diagnosis of AIH, the first sign is increased titers of the AFP oncomarker, often detected in screening. It is necessary to consider that AIH can occur under the mask of other clinical signs for several years and can be mistakenly regarded as SLE, rheumatoid arthritis, which is a prerequisite for determining AIH markers [1, 2, 3, 4, 7, 8].

Table 3

Autoimmune hepatitis blood immunological results from 23.03.2020 г.

Variable	Result	Valeurs de reference
Immunoglobulin G (IgG), g/L	30,67	7-16
Antinuclear antibodies IgG (ANA IgG)	Положительный	Отрицательно
Smooth muscle antibodies (S-SMA), IgG +A +M	1:160	< 1:100
Anti-liver kidney microsomal (aLKM), IgG +A + M	< 1:40	< 40

If AIH is verified to be highly active with positive markers, early initiation of pathogenetic therapy is necessary, despite the absence of results of liver morphological analysis (biopsy). At the same time, it is necessary to consider the risk of hepatic complications in response to treatment with glucocorticosteroids, development of systemic inflammatory reaction. Genetically engineered biologics and liver transplantation can be an alternative therapy option.

If AIH is verified to be highly active with positive markers, early initiation of pathogenetic therapy is necessary, despite the absence of the results of morphological analysis of the liver (biopsy). At the same time, it is necessary to consider the risk of hepatic complications in response to treatment with glucocorticosteroids, development of systemic inflammatory reaction. Genetically engineered biologics and liver transplantation can be an alternative therapy option. The presented clinical observation demonstrates the necessity of early diagnosis for exclusion of AIH in predisposed patients, timely and competent use of systemic and topical immunosuppressive therapy and decision on the indication of alternative therapy as indicated.

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