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Extrahepatic manifestations associated with chronic hepatitis C infections in Poland

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ABSTRACT

Purpose: To assess the prevalence and predictive factors of extrahepatic manifestation (EM) in patients with chronic hepatitis C (CHC) infection in Poland.

Material and Methods: 340 consecutive patients (mean age: 42 years) with untreated CHC were studied between 2000 and 2006. The HCV infection was defined by positive serology and serum HCV RNA. The inflammation grade and fibrosis stage were assessed according to Ishak. Demographic, laboratory and liver biopsy data were collected. The patients with liver cirrhosis, concomitant HBV or HIV infection, autoimmune liver diseases and alcohol abusers were excluded from the analysis.

Results: 210 patients with CHC (61.7%) presented at least 1 extrahepatic manifestation, including mixed cryoglobulinemia (37.1%), thrombocytopenia (27.6%), thyroid autoimmunity (16.2%), dermatological disorders (4.1%) and type 2 diabetes (4.1%). Other EM such as the sicca syndrome, nephropathy, polyneuropathy and B-cell lymphoma were observed in single cases. In multivariate analysis lower platelet count was found as a predictive factor of EM in patients with CHC.

Conclusions: The majority of patients with CHC, living in Poland, have EM, of which cryoglobulinemia, thrombocytopenia, thyroid autoimmunity, dermatological disorders and type 2 diabetes are most common. Through the multivariate analysis the lower platelet predicts extrahepatic manifestations associated with chronic hepatitis C.

Key words: hepatitis C, extrahepatic manifestation, cryoglobulinemia, thrombocytopenia, thyroid autoimmunity

INTRODUCTION

Hepatitis C virus (HCV) affects approximately 3% of the population worldwide and is a leading cause of the chronic liver disease. HCV is hepatotropic but its manifestations can extend beyond the liver. A wide variety of extrahepatic manifestations (EM) has been reported to be associated with the chronic hepatitis C infection (CHC), including mixed cryoglobulinemia, thrombocytopenia, aplastic anemia, autoimmune thyroiditis, arthropathy, membranoproliferative glomerulonephritis, peripheral neuropathy, skin disorders such as lichen planus or porphyria cutanea tarda, sicca syndrome, type 2 diabetes, Mooren ulcer's of the eye and others [1-3].

Most of the extrahepatic manifestations are of lymphoproliferative or autoimmune nature, and they are thought to be related to immune-mediated mechanisms. Patients with CHC commonly have immunologic features, including circulating autoantibodies and deposits of immune complexes in various tissues outside the liver. This may represent a major pathogenic pathway for extrahepatic disorders in the course of HCV infection. It has also been suggested that a direct infection of cell population around the liver by HCV may play a role in determining some EM. This hypothesis is supported by a possible HCV replication in extrahepatic tissue such as bone marrow, central nervous system, endocrine glands, lymph nodes, spleen, monocytes, macrophages or skin cells. In some of these manifestations, an epidemiological ground

is established whereas pathogenic mechanisms are not fully explained [2,4,5].

Until now, no survey has been conducted in Poland in a large monocenter cohort to estimate the frequency of different extrahepatic disorders in the course of the chronic hepatitis C. Therefore the aims of the present study were to assess the prevalence of clinical and biological extrahepatic manifestations associated with the chronic HCV infection and to determine the predictive factors of their occurrence in patients in a mono-center cohort in Poland.

MATERIAL AND METHODS

Three hundred and forty previously untreated chronic hepatitis C patients (pts) consecutively evaluated at the Infectious Diseases Unit of Provincial Hospital in Kielce from January 2000 to December 2006. The study group consisted of 134 women and 206 men. The diagnosis of the chronic HCV infection was based on elevated serum aminotransferases levels (persistent or fluctuating), positive testing for serum anti-HCV and HCV RNA, and was confirmed by the the liver biopsy. The patients with cirrhosis, HBV and/or HIV co-infection, autoimmune liver diseases, other serious chronic illnesses, as well as patients with history of alcohol abuse, were excluded from the analysis. The demographic, laboratory and liver biopsy data were obtained from all patients at the time of evaluation. The putative duration of HCV infection was estimated from the date of transfusion or initial exposure to other parenteral sources; it was not assessed in patients with a sporadic infection of unknown origin. The study was approved by the Ethical Committee of Medical University in Bialystok, Poland.

The serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl transpeptidase (GGT), thyrotropic hormone (TSH), blood glucose, bilirubin and hemoglobin concentration, platelet and leucocyte counts were assayed with using standard methods.

The test for HCV antibodies was performed with the third-generation enzyme-linked immunoassay (ELISA).

HCV RNA qualitative and HCV genotype was determined by RT-PCR method using a COBAS AMPLICOR HCV v. 2.0 (Roche Diagnostic Inc.).

The inflammation grade and fibrosis stage in the liver specimens were scored according to Ishak et al. [6].

The diagnosis of extrahepatic manifestations was based on clinical and laboratory data as follows:

The cryoglobulins were detected using the precipitation method; serum samples for the presence of cryoprecipitate were collected and separated at 37°C, then stored at 4°C for 7 days; the cryoglobulins were measured in 305 patients (89.7%).

The thrombocytopenia was defined as a platelet count below 140 x 10^9/l on two separate occasions tests.

The diabetes was diagnosed if the fasting blood glucose exceeded 126mg/dl on two separate measurements.

The thyroid autoimmunity was defined as elevated serum anti-thyroid peroxidase antibody (anti-TPO) (reference 0-60U/ml) and anti-thyroglobulin antibody (anti-TG) (reference 0-60U/ml) titers evaluated by immunoradiometric assays in sera from 259 patients (76.1%).

The sicca syndrome was diagnosed if a patient's subjective complaints (ocular and oral dryness) were confirmed by the laryngologic and ophthalmologic examinations including Schirmer's test.

The diagnosis of glomerulonephritis was confirmed by kidney biopsy.

Skin disorders were diagnosed through the examination of skin, oral mucosa, hair and nails.

The diagnosis of B-cell lymphoma was established by a hematologist on the basis of morphologic evaluation of bone marrow specimens.

Statistical analysis

The measurable data was presented as the mean ± standard deviation (SD), the percentage distribution was assessed for qualitative characteristics. The statistical analysis was performed with Mann-Whitney, Fisher exact and rank Spearman tests. An assessment of characteristics of HCV infection associated with the extrahepatic manifestations was performed using univariate and multivariate (logisitc regression) analyses. The statistical significance was accepted at $p<0.05$.

RESULTS

The mean age of patients was 41.8±13.8 years (range 18-73). The mean putative duration of HCV infection (15.1±9.2 years) was estimated in 307 pts. The route of HCV transmission was evaluated for 320 patients, of which 40.3% (129 pts) had a blood or blood component transfusion before 1992, 31.2% (100 pts) had a history of a surgery, the remaining potential sources of HCV infection include dental procedure, endoscopy, intravenous drug use and tatoo. Twenty patients of total 340 (6%) did not have such risk factors.

All patients were serum HCV RNA positive, the HCV genotype was assessed in 242 patients (71.2%). Most of them – 197, were infected with genotype 1 (81.4%); 38 pts (15.7%) with genotype 3; 4 pts (1.7%) belonged to genotype 4 and in 3 pts (1.2%) the mixed genotype was determined.

At least one extrahepatic manifestation was identified in 210 pts (61.7%). Three manifestations had a prevalence > 4%, including, in decreasing order, mixed cryoglobulinemia (37.1%), thrombocytopenia (27.6%), thyroid autoimmunity (16.2%), dermatological disorders (4.1%) and type 2 diabetes (4.1%). Other EM such as sicca syndrome and nephropathy had a much lower prevalence; polyneuropathy and B-cell