# EXTRAHEPATIC MANIFESTATIONS IN CHRONIC HEPATITIS C

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***Keywords:*** *chronic hepatitis C, extrahepatic manifestations*

***Abstract:*** *Chronic hepatitis C is a frequently encountered problem worldwide, the number of infected individuals is high and continues to be, becoming a public health problem. In Romania, there are nearly 1 million persons infected with hepatitis C virus, the magnitude of its spread being related to specific risk factors. Among the hepatic manifestations, in chronic hepatitis C, there also occur other extrahepatic manifestations, such as mixed cryoglobulinemia (sometimes, associated with membranoproliferative glomerulo-nephritis), as well as other endocrine manifestations (diabetes mellitus, hypothyroidism), haematological manifestations – aplastic anemia, thrombocytopenia purpura, lymphomas. In accordance with recent studies, lichen planus, chronic urticaria, corneal ulceration, uveitis and lung fibrosis represent other extrahepatic manifestations. These manifestations are rare.*

## INTRODUCTION

An important number of infections with hepatitis C virus (HCV) present simultaneous extrahepatic manifestations proved to be the single manifestation and its detection is important for diagnosis and treatment.

The association between infection with hepatitis C virus and extrahepatic manifestations is important to be recognized for adequate diagnosis tests.

Knowing extrahepatic manifestations of hepatitis C virus infection and the confirmation of the simultaneous presence of hepatitis C virus allow applying a medical treatment which often determines the improvement of extrahepatic manifestations.

## PURPOSE

I analyzed the distribution of chronic hepatitis C virus in the General Hospital of Sibiu, between 1 January 2009 and 1 January 2012, the aim of study being to establish the characteristics and the frequency of extrahepatic manifestations.

At the same time, I aimed at establishing the correlations between age, gender, residence, the possible infection moment and extrahepatic manifestations.

## MATERIALS AND METHODS

The study is a retrospective one based on 162 cases of chronic hepatitis with positive HCV antibodies hospitalized in the General Hospital of Sibiu. 78 cases with chronic hepatitis C were followed up prospectively during hospitalization.

Each patient had a clinical observation sheet with personal data, personal pathological and heredity history, anamnesis and clinical data, the results of lab tests and paraclinical investigations.

The test which was used for evidence of the HCV antibodies was generation II or III ELISA (Murex anti-HCV-versions III, Menolisa (R) anti-HCV PLUS, ORTHO (R) HCV 3.0 ELISA). There were recorded the onset of the clinical manifestations, the moment of diagnosis, the way of tracing out the infection with hepatitis C virus, epidemiological inquiry in order to establish the possible infection moment. All information was based on personal assertions.

For each patient, there was made a short case presentation in order to highlight the particular aspects of diagnostic, evolution and treatment.

The inclusion criteria were the following:

- patients with hepatitis C infection confirmation by ELISA (II or III generation), with hepatic and extrahepatic manifestations.

The exclusion criteria were the following:

- patients with simultaneous infection with hepatitis B virus and HIV;
- patients with alcoholic hepatitis;
- patients with autoimmune hepatitis or with autoimmune manifestations;
- patients with liver cirrhosis and hepatocellular carcinoma, with hepatitis C virus infections confirmed by ELISA generation II or III.

The diagnosis of chronic hepatitis C virus was established by:

- anamnesis criteria (epidemiological inquiry);
- clinical criteria;
- laboratory criteria (hepatic functional test and aetiological confirmation);
- hystopathological criteria.

## RESULTS

The group of 162 cases with chronic hepatitis with positive HCV antibodies included 102 females (63%) and 60 males (37%).

In this study, I noticed that the affection tended to be preponderant in the age group of 60 – 69 years old (27.16%), followed by the age group of 50 – 59 years old (25.92 %), with a p value of 0.0668.

The average age was 54.46±13.15 years. Of the group, 132 patients came from the urban environment (81%) and 30 patients from the rural environment (19%).

53 patients (33%) had hepatic manifestations and extrahepatic manifestations, and 109 patients presented only hepatic manifestations – figure no 1.

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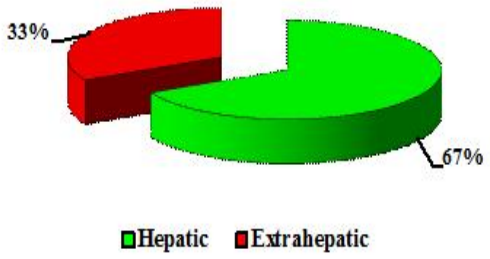
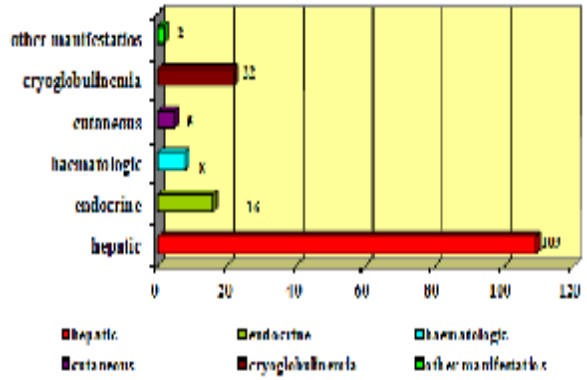
**Figure no. 1. Distribution of the group of patients according to hepatic and extrahepatic manifestations**




The distribution of cases with extrahepatic manifestations was the following: 16 patients had endocrine manifestations (30.18%), p value = 0.008; Odds ratio = 0.43 and the Relative risk = 0.58; 22 patients had cryoglobulinemia (41.53%), p value = 0.085; Odds ratio = 0.62 and Relative risk = 0.73; 5 patients presented skin manifestations (9.43%), p value = 0.0000044; Odds ratio = 0.14 and Relative risk = 0.21; 8 patients had hematological manifestations (15.09%), p value = 0.00006; Odds ratio = 0.22 and Relative risk = 0.33; and 2 patients had other manifestations (3.77%), p value = 0.0000002; Odds ratio = 0.06 and Relative risk = 0.09 – figure no. 2.

**Figure no. 2. Patients' distribution depending on the type of extrahepatic manifestations**




One third of patients presented extrahepatic manifestations which showed the high frequency of extrahepatic manifestations – table no. 1.

**Table no. 1. Patients' distribution depending on the type of extrahepatic manifestations**

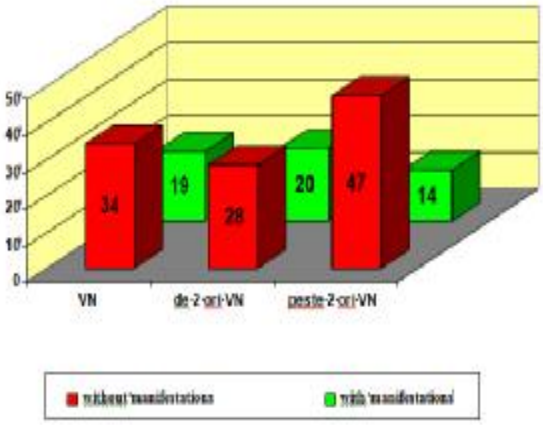
| Extrahepatic manifestations | Number of cases | Percentage |
|---|---|---|
| ***ENDOCRINE MANIFESTATIONS*** | | |
| Diabetes mellitus without insulin | 11 | 20.75 % |
| Diabetes mellitus with insulin | 2 | 3.77 % |
| Thyroiditis | 1 | 1.88 % |
| Hypothyroidism | 2 | 3.77 % |
| ***p value = 0.008; Odds ratio = 0.43; 0.23<OR<0.86 and Relative risk = 0.58; 0.37<RR<0.91*** | | |
| ***CRYOGLOBULINEMIA*** | | |
| Mixed crioglobulinemia | 17 | 32.17 % |
| Chronic glomerulonephritis associated with impure nephrotic syndrome | 1 | 1.88 % |
| Chronic glomerulonephritis membranoproliferative | 2 | 3.77 % |
| Vascular purpura | 2 | 3.77 % |
| ***p value = 0.085; Odds ratio = 0.62; 0.34<OR<1.11 and Relative risk = 0.73; 0,5<RR<1.07*** | | |
| ***CUTANEOUS MANIFESTATIONS*** | | |
| Chronic urticaria | 1 | 1.88 % |
| Porphyria cutanea tarda | 1 | 1.88 % |
| Vitiligo | 1 | 1.88 % |
| Lichen planus | 2 | 3.77 % |
| ***p value = 0.0000044; Odds ratio = 0.14; 0.05<OR<0.38 and Relative risk = 0.21; 0,09<RR<0.5*** | | |
| ***HAEMATOLOGICAL MANIFESTATIONS*** | | |
| Immunoblastic lymphoma | 1 | 1.88 % |
| Malignant lymphoma nonhodgkinian | 3 | 5.66 % |
| Acute lymphoblastic leukosis ($ALL_2$) | 1 | 1.88 % |
| Acute myeloid leukemia ($AML_2$) | 1 | 1.88 % |
| Chronic lymphoproliferative syndrome | 2 | 3.77 % |
| ***p value = 0.00006; Odds ratio = 0.22; 0.09<OR<0.51 and Relative risk = 0.33; 0.17<RR<0.63*** | | |
| ***OTHER MANIFESTATIONS*** | | |
| Pulmonary fibrosis | 1 | 1.88 % |
| Rheumatoid arthritis | 1 | 1.88 % |
| ***p value = 0.0000002; Odds ratio = 0.06; 0.01<OR<0.24 and Relative risk = 0.09; 0.02<RR<0.36*** | | |

In accordance with specialized literature, vascular purpura, chronic glomerulo-nephritis with impure nephrotic syndrome, membranoproliferative glomerulo-nephritis and manifestation of mixed cryoglobulinemia were present in 22 cases (41.53%), p value = 0.085.

The most frequent extrahepatic manifestations in the study group was mixed cryoglobulinemia, both symptomatic – 5 cases (9.43%) and asymptomatic – 17 cases (32.17%), followed by diabetes mellitus without insulin – 11 cases (20.75%).

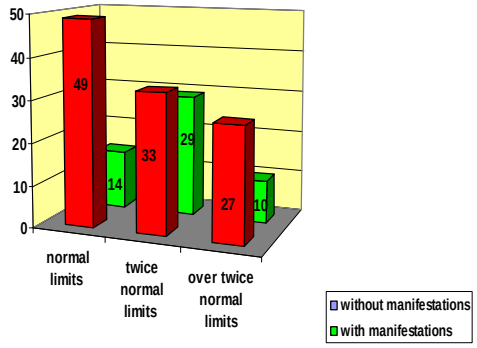
Analyzing alanine aminotransferase (ALAT) level, in the most cases with extrahepatic manifestations, ALAT level was in normal limits – 19 cases (35.84%) and to twice normal limits in 20 cases (37.74%) and over twice normal limits – 14 cases (26.42%) – figure no. 3.

**Figure no. 3. Group distribution depending on the value of ALAT**



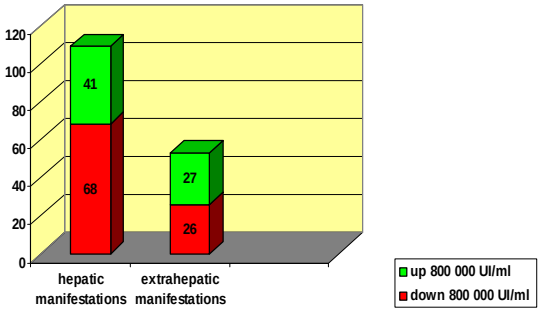

Analyzing aspartate transaminase (ASAT) level, the most cases with extrahepatic manifestations had ASAT in normal limits – 14 cases (26.42%) and to twice normal limits 29 cases (54.72%) and over twice normal limits – 10 cases (18.86%) – figure no. 4.

**Figure no. 4. Distribution of the group of patients depending on the value of ASAT**




Analyzing the transfusion history, 9 cases (6%) received blood transfusion and 90 patients (56%) had surgery history. Analyzing the viral load in the cases with hepatic and extrahepatic manifestations, it was shown that the viral load below 800 000 UI/ml was registered in 68 patients (62.38%) with hepatic manifestations versus 26 patients (49%) with extra-hepatic manifestations and viral load above 800 000 UI/ml was registered in 41 patients (37.62%) with hepatic manifestations versus 27 patients (51%) with extrahepatic manifestations, p value = 0.1; Odds ratio = 0.58 and Relative risk = 0.83 – figure no. 5.

**Figure no. 5. Patients' distribution according to viral load**




In this study, there were no significant statistical differences in fibrosis stage in the patients with hepatic manifestations and extrahepatic manifestations. Also, there was no correlation between viral load and extrahepatic manifestations, meaning that a high viral load to be correlated with lesions other than the hepatic ones.

By comparing the results of therapy in the patients with hepatic and extrahepatic manifestations, it was shown that 30 patients (58.83%) with hepatic manifestations had incomplete response versus 10 patients (26.32%) with extrahepatic manifestations; 11 patients (21.54%) with hepatic manifestations presented a complete response versus 3 patients (7.89%) with extrahepatic manifestations and 10 patients (19.63%) with hepatic manifestations had no response versus 25 patients (65.79%) with extrahepatic manifestations – table no. 2.

**Table no. 2. Group distribution depending on the response to treatment in patients with hepatic and extrahepatic manifestations**

| Type of response | Hepatic manifestations | Extrahepatic manifestations |
|---|---|---|
| Incomplete | 30 (58.83 %) | 10 (26.32%) |
| Complete | 11 (21.54 %) | 3 (7.89%) |
| Lack of response | 10 (19.63 %) | 25 (65.79%) |

The most patients had rebound in the first 6 months, subsequently, until the end of the follow-up period of time, the number of relapses was very low. The clinical response was in parallel with the immunological response, the values being compatible.

## DISCUSSIONS

An important aspect of chronic infection with hepatitis C represents its association with a number of extrahepatic manifestations.(1) Almost 40% of patients infected with HCV develop at least one extrahepatic manifestation during the disease.(2)

Extrahepatic manifestations are diseases or conditions that affect other organs besides the liver. Extrahepatic manifestations of HCV can be found in the skin, eyes, joints, immune system, nervous system and kidneys. Among them, the most important, but the most common, is mixed cryoglobulinemia.

Pascual et al. (3), for the first time in 1990, suggested an association between HCV and extrahepatic syndromes when they presented two patients with HCV infection and mixed cryoglobulinemia. In some of these, such as mixed cryoglobulinemia, it was established that there is a direct involvement of HCV in the disease, in other cases, this relation cannot be established.(4)

In the study conduced by Alan Franciscus, it was determined that 74% of patients with chronic hepatitis C showed extrahepatic manifestations. Some of the reported events were: arthralgia (74%); tingling in limbs (17%); myalgia (15%); pruritus (15%), and sicca syndrome (11%).(5)

Extrahepatic manifestations in the studied group of patients with chronic hepatitis C were present in one third of them, which indicates that extrahepatic manifestations occur with increased frequency. According to the literature, the study shows that vascular purpura, chronic glomerulonephritis associated with nephrotic syndrome impure, chronic membranoproliferative glomerulonephritis and mixed cryoglobulinemia manifestations were present in 22 cases (41.53%), the data obtained were statistically significant (p value = 0.085; Odds ratio = 0.62; 0.34<OR<1.11 and Relative risk = 0.73; 0.5<RR<1.07).

The most common extrahepatic manifestations in the studied group was mixed cryoglobulinemia, both symptomatic form – 5 cases (9.43%) and asymptomatic – 17 cases (32.17%), followed by type 2 diabetes without insulin – 11 cases (20.75%).

The literature reported two cases of tongue carcinoma and HCV infection known for 6 and 10 years with oral cancers detected in tissues of RNA chains + and - of HCV in 100% and 71%.

In the present study, I have not encountered any cases of tongue cancer, but there were 4 cases of tumours of other location: vaginal tumour – 1 case (1.88%); lung cancer – 1 case (1.88%); rectal tumour – 1 case (1.88%); a tumour of the bladder – 1 case (1.88 %). In the literature, there were not reported cancers with these locations associated to chronic infection with hepatitis C virus.

Also, the data in the literature show that sialadenitis occurs in 57% of patients infected with hepatitis C virus (6,7), but in this study, there was not detected any event, although clinical symptoms occurred in 8 cases, but without establishing the diagnosis, probably due to the lack of necessary examinations (biopsy, sialography and scintigraphy of the salivary glands).

My observation is that antiviral treatment may improve the clinical picture of vasculitis, even in the absence of sustained virologic response. The disappearance of

cryoglobulins in patients who have not achieved virologic response may be due to their marked quantitative reduction to undetectable levels by ordinary means.

## CONCLUSIONS

- The extrahepatic manifestations were present in one third of patients, meaning that extrahepatic manifestations appear with a high frequency.
- The most frequent extrahepatic manifestations was: mixed cryoglobulinemia, both symptomatic (9.43%) and asymptomatic (32.17%), followed by diabetes mellitus without insulin (20.75%). In accordance with specialized data, mixed cryoglobulinemia is the most frequent extrahepatic manifestations, which is also confirmed in this study.
- Chronic hepatitis C is frequently associated with extrahepatic manifestations, the most frequent extrahepatic manifestation is mixed cryoglobulinemia. If in some of extrahepatic manifestations, the role of HCV is well established, in others, it is still speculative. The number of extrahepatic manifestations in chronic hepatitis C continues growing and has become an open field of research.

## REFERENCES

1. Conjeevaram HS, Wahed AS, Afdhal N, et al. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. Gastroenterology. 2011;140:469.
2. Lo Re V 3rd, Volk J, Newcomb CW, et al. Risk of hip fracture associated with hepatitis C virus infection and hepatitis C/human immunodeficiency virus coinfection. Hepatology. 2012;56:1688
3. Ennishi D, Maeda Y, Niitsu N, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood. 2010;116:5119.
4. Ramos – Casals M, Font J. Extrahepatic manifestations in patients with chronic virus infection. Current Opinions on Rheumatology. 2005;17(4):447-55.
5. Franciscus A. A guide to extrahepatic manifestations of hepatitis C. HCSP FACTsheet. 2005;1-3.
6. Liu SQ, Dong MG, Men CH, Yang MJ, Liu W. Relation research between chronic hepatitis C and type 2 diabetes (in Chinese). J Pract Diagn Ther. 2011;25:83-84.
7. Zheng YY, Fan XH, Wang LF, Tian D, Huo N, Lu HY. Efficacy of pegylated interferon – alpha – 2a plus ribavirinum for patients aged at least 60 years with chronic hepatitis C. Chin Med J. 2012;125:1852-56.