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Original Article

Rheumatologic Manifestations in Hepatitis C Patients: A Multicentric Study

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Abstract.

Introduction: The World Health Organization (WHO) has estimated that about 180 million people are infected with the Hepatitis C virus (HCV). One in every 20 Pakistanis has been already infected with this infection. With confusing rheumatological signs and symptoms of arthritis and Hepatitis C, timely diagnosis and treatment have become a challenge for clinicians.

Objectives: This study aims to determine the Rheumatological Manifestations in Patients diagnosed with Hepatitis C, and to investigate the relationship of rheumatological manifestations with the chronicity of hepatitis C.

Material and methods: The cross-study was carried out at hepatology clinics of the three allied public sector hospitals situated in Rawalpindi for 2 years due to the pandemic. 114 patients of either gender were recruited. Patients were evaluated for different rheumatological features throughout history and examination. Patients with Hepatitis C, HCV positive were included and patients with HBV and Paraneoplastic syndrome, previously known as musculoskeletal disease, CKD, DM, were excluded.

Results: Out of 114 patients, 52 were male and 62 females. Duration of diagnosis of 37 patients less than 6 months and of 77 patients more than 6 months. The study showed a significant relation between duration since diagnosis(chronicity) and positive ultrasound findings, including fatty liver and cirrhosis, arthralgias, sicca symptoms, numbness and paresthesia and a significant relation between inflammatory arthritis and ALT levels. SICCA symptoms manifestation also showed a significant relation with a high SSS fibromyalgia score and high bilirubin levels.

Conclusions: With chronicity of Hepatitis C, patients manifested more Rheumatological signs and

symptoms confusing the diagnosis with rheumatoid arthritis.
Keywords: Rheumatic Diseases, Hepatitis C, Hepatitis C Chronic.

Introduction

The World Health Organization estimates that 58 million people worldwide have chronic hepatitis c virus (HCV) infection, with 10 million infected people in the Southeast Asia region.[1]Pakistan bears the second highest global burden of hepatitis C virus (HCV) infection, with 5% of the population infected (i.e., 8 million people). [2] Moreover, in Pakistan, rheumatic diseases afflict all age groups, particularly patients 18-40 years old. [3]Besides the primary liver infection, HCV leads to several extrahepatic clinical findings, including rheumatic, hematological, renal, dermatological, neurological, and other systemic autoimmune disorders.[4]

The strong association between HCV infection and rheumatic diseases such as mixed cryoglobulinemia or other vasculitides, rheumatoid arthritis (RA), systemic lupus erythematosus, fibromyalgia (FM), Sjögren syndrome, and other rheumatic conditions has been extensively described in literature.[5]It has been hypothesized that these manifestations result from viral invasion of lymphoid cells, immune dysregulation, and the consequent production of non-organ—specific autoantibodies (such as rheumatoid factor and cryoglobulin) and inflammatory markers (such as IL-6).[6,7]

It remains a challenge to differentiate between rheumatic symptoms such as arthralgia and arthritis caused by HCV primary chronic infection and those secondary to rheumatic disease development. However, it is imperative to make this distinction as the management and prognosis of both are a different, and specific treatment against the virus may decrease or bring an end to rheumatic symptoms.[8]

Rheumatic complaints could be the first manifestations of an otherwise asymptomatic hepatic HCV infection, leading to a late hepatitis diagnosis which may increase the likelihood of complications.[9, 10] Therefore, this study aimed to assess the frequencies of rheumatological findings in patients infected with HCV treated at hepatology clinics of the three allied public sector hospitals situated in Rawalpindi: Holy Family Hospital, Benazir Bhutto Hospital and District Head Quarter Hospital.

Materials and Methods

This was a cross-sectional study conducted from 10th June 2019 to 10th June 2020 at the Hepatology clinics of the three allied public sector hospitals situated in Rawalpindi: Holy Family Hospital, Benazir Bhutto Hospital, and District Head Quarter Hospital after the institutional ethical approval was taken from Institute Research Forum. Non-probability consecutive sampling technique was used to recruit 114 patients. Verbal informed consent was obtained from all participants and confidentiality was assured. Male and female patients with chronic hepatitis C infection (diagnosed through the presence of antibodies to the hepatitis C virus and confirmed by positive PCR for hepatitis C virus RNA) were included in the study. Patients with hepatitis B virus infection, paraneoplastic syndrome, previously diagnosed musculoskeletal disease,

chronic kidney disease, and diabetes mellitus, were excluded. The sample size was calculated to be 114, for a confidence level of 95% and a margin of error of 5%, based on the prevalence of rheumatological manifestations in hepatitis C patients[13]. Patients were assessed by taking complete history and general and rheumatological examination. Duration of hepatitis, presence of myalgias, arthralgias, arthritis, pattern of joint involvement (mono, oligo, or polyarticular), inflammatory or mechanical arthritis, and duration of morning stiffness were asked. The history of Raynaud's phenomenon, rash on the body, paraesthesia, numbness, and dryness of eyes and mouth was taken. Patients were evaluated for fibromyalgia using the widespread pain index (WPI) and the symptom severity scale (SSS). Those who had a WPI score of seven or higher, an SSS score of five or higher, a WPI score of three to six, and an SSS score of nine or higher, were diagnosed with fibromyalgia. Liver ultrasonography was used to assess fatty liver and liver cirrhosis.

The data was analyzed using statistical software program SPSS version 25.0. Frequencies and percentages were calculated for categorical data like sex of the patient, level of education, duration of hepatitis, presence of arthralgia, inflammatory arthritis, degenerative arthritis, Raynaud's phenomenon, paraesthesia, numbness, sicca symptoms, fatty liver and cirrhosis on ultrasound, and duration of early morning stiffness. Mean and standard deviation were calculated for numerical data like age, WPI, and SSS score. The Chi-square test was used to check for any significant associations between categorical variables. Kruskal Wallis and Mann-Whitney U tests were used to assess any significant differences between mean values. A p-value<0.05 was considered to be significant.

Results

Out of 114 patients, 52 were male and 62 were female. The diagnosis for 37 patients was less than 6 months and over 6 months for 77 patients (Table 1).

Table-I Demographics

Patient details		**Frequency**
Mean Age		46.62+13.44
Sex	Male	52
	Female	62
	Total	114
Duration since diagnosis	<6 months	37
	>6 months	77

The most common rheumatological manifestation in Hepatitis C positive patients was paresthesia (71.9%), followed by numbness (69.3%). The frequencies of the various parameters are depicted in Table 2.

Table-II Frequency of Rheumatological presentations in Hepatitis C patients

Rheumatological Features		Frequency	Percentage (%)
Arthralgias	Small joints	2	1.8
	Large joints	40	40.4
	Both	41	41.2
Paresthesias		72	71.9
Numbness		69	69.3
Fibromyalgias	WPI Mean Score	12.16+4.13	-
	SSS Mean Score	7.21+2.31	-
Raynauds		11	11.8
SICCA symptoms		12	51.0
Inflammatory Arthritis	Mono	24	30.0
	Oligo	18	22.0
	Poly	12	15.6
EMS Duration	<1 hr	43	43.0
	>1 hr	27	27.2
Degenerative arthritis		4	3.5
Ultrasound	Mild Fatty Liver	18	17.5
	Cirrhosis	26	26.3

Chi-Square test performed showed significant association between duration since diagnosis (chronicity) and positive ultrasound finding of fatty liver and cirrhosis (p=0.07), arthralgias (p=0.022), sicca symptoms (p=0.025), numbness (p=0.025) and paresthesia (p=0.003) (Figure 1).

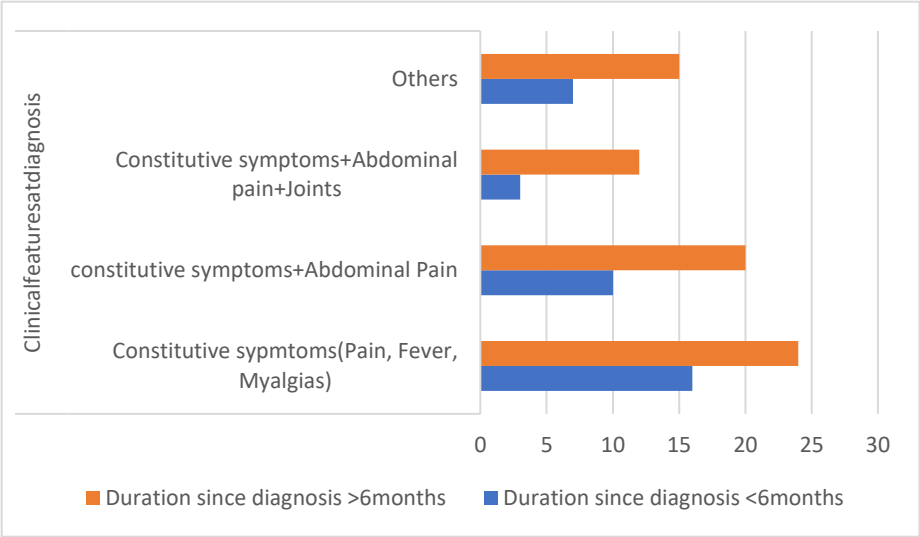

Figure 1: Comparison of duration of diagnosis with clinical features at diagnosis.

The Kruskal-Wallis test performed showed a significant relation between inflammatory arthritis and ALT levels. SICCA symptoms manifestation was also significantly associated with a high SSS fibromyalgia score (p=0.08) and high bilirubin levels (p=0.016). The relation between Early Morning Stiffness duration and high SSS fibromyalgia score calculated via the Mann-Whitney test achieved statistical significance (p=0.07).

Discussion

Rheumatological manifestations are frequently encountered during the course of hepatitis C infection. In our study, patients with chronic hepatitis C infection reported most commonly with arthralgias (83.4%) followed by paresthesia (71.9%), numbness (69.3%), sicca symptoms (51.0 %), and Raynaud's phenomena (11.8%). A large majority of the patients were diagnosed with fibromyalgia (79.0%) and inflammatory arthritis (67.6%) which was most commonly monoarticular. The findings are consistent with a Brazilian Study that assessed the rheumatological manifestations in patients suffering from Hepatitis B or C in a reference unit. Arthralgia was reported in 90.6% of patients who were suffering from Hepatitis C. Other positive findings were myalgia (65.6%) and arthritis (40.6%) of the patients. [11] Similarly, another study done in Tunisia reported polyarthralgia of big joints (88.15 %), myalgia (14.47 %), and dryness syndrome (22.36 %) in chronic hepatitis C patients.[12]

Contrary to our results, a local study conducted at the Pakistan Institute of Medical Sciences, Islamabad, reported a much lesser percentage of arthralgia (49%), paresthesia (22%), numbness (46%), fibromyalgia (33%), and arthritis (18%) which was most commonly oligoarticular, compared to the present study.

[13]In a large prospective study of 1612 patients with chronic HCV infection, rheumatic manifestations were found in 31%, the most prevalent being arthralgias (9%), arthritis (4%), sicca symptoms (8%), and myalgias (24%). [14] Another recent study conducted in Egypt reported rheumatic manifestations associated with HCV infection to be present in only 16.39% of patients, with arthralgias in 6.5% and fibromyalgia in 1.9% of the patients. [15] A study conducted in France reported arthritis in 42.8% and 12.2% of patients attending rheumatology clinics and members of HCV support associations respectively. [16,17,18] The lesser prevalence of rheumatic manifestations in the older studies could be due to the difference in study setting. These studies had participants from a single center, whereas our study was multicentric.

In our study, a significant association was found between duration since diagnosis (chronicity) of hepatitis C infection and rheumatological manifestations like arthralgias, sicca symptoms, numbness, and paresthesia, which is following previous studies. This makes the early diagnosis and treatment of hepatitis C imperative not just for the prevention of hepatic complications like hepatocellular carcinoma, but also for the common rheumatic manifestations shown in this study. Current guidelines recommend screening patients with rheumatic disease manifestations for hepatitis b and c and treating positive patients with appropriate oral antivirals.[8]Treatment and management guidelines should be revised to inculcate the role of a multi-disciplinary team rather than just gastroenterologists in managing patients suffering from chronic hepatitis C disease. The high prevalence of rheumatological manifestations found in patients with hepatitis C infection emphasizes the importance of considering viral hepatitis as the differential diagnosis for patients with rheumatic symptoms and also of hepatitis serological testing as a routine investigation protocol for rheumatic diseases. The limitations of our study were the possible selection bias, that rheumatic findings were not further confirmed using imaging modalities like X-rays, and that serum anti-CCP antibodies were not checked to rule out rheumatoid arthritis.

Conclusion

There is a high prevalence of rheumatological manifestations in patients with hepatitis C infection.

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