

Original Article

Rheumatological Manifestations of Hcv Infection at a Tertiary Care Hospital

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Objective: To determine the frequency of different rheumatic manifestations of hepatitis C infection in a tertiary care hospital.

Study design: Observational cross sectional study.

Place and duration: Study was conducted at Rheumatology and Gastroenterology department of Pakistan Institute of Medical Sciences, Islamabad, between August 2010 and May 2011.

Subjects and Methods: Patients of either gender over 16 years of age with hepatitis C virus infection attending Gastroenterology clinic were recruited. Patients were evaluated for different rheumatic features through history, general physical and rheumatological examination followed by relevant investigations.

Results: Out of a total of 100 patients there were 37(37%) males and 63 (63%) females. The mean age was 41.39 ± 10.19 years. Myalgias were the most common found in 79% followed by arthralgias in 49%, fibromyalgia 33%, Raynaud's phenomenon 11%, paraesthesia 22%, numbness 46%, neuropathy 3%, vasculitis 0%, dry Eyes 4% and dry mouth in 32% of patients. Inflammatory arthritis was present in 14 patients. High titers of antiCCP antibodies were found in 3 patients who met the ARA criteria for rheumatoid arthritis. Low titers of antiCCP antibodies were present in 2 patients.

Conclusion: HCV infected patients reported a wide variety of rheumatological manifestations. Myalgia, arthralgia, sicca symptom, fibromyalgia, arthritis, Raynaud's phenomenon were the predominant features. AntiCCP antibodies can occasionally be found in low titers in patients of HCV infection with articular symptoms.

Key Words: Hepatitis C, Cyclic citrullinated peptide, arthritis.

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Introduction

Hepatitis C is a major public health concern worldwide.¹ Over 200 million people around the world are infected with hepatitis C - an overall incidence of around 3.3% of the world's population. In a recent sero- prevalence study by PMRC (Pakistan Medical Research council) it is reported that 8.8 million people in Pakistan are suffering from hepatitis C. High prevalence of hepatitis C has been reported in the largest province of Pakistan.² Eighty percent of the patients infected by Hepatitis C develop chronic infection and 20% of them will go on to develop hepatic cirrhosis and 3-5% hepatocellular carcinoma.¹

Besides hepatic complications of Hepatitis C there are various extra hepatic manifestations.^{1, 3, 4, 5, 6} Rheumatic manifestations are present in 20 % of the patients with

hepatitis C.¹ These include myalgias, arthralgias, arthritis, fibromyalgia and cryoglobulinemic vasculitis. Hepatitis C related arthritis may present as monoarthritis, oligoarthritis and polyarthritis resembling rheumatoid arthritis.^{4, 7, 8} Oligoarthritis is usually associated with cryoglobulinemia.^{3, 4}

Polyarthritis related to hepatitis C may be indistinguishable from rheumatoid arthritis and sometimes may fulfill the ARA criteria for rheumatoid arthritis.^{3, 8} Rheumatoid factor is not a reliable serological test to distinguish Hepatitis C related arthritis from RA because it is frequently found in the patients with hepatitis C.^{3, 8} Anti CCP Antibodies have been identified to reliably differentiate between the two types of arthritis in various studies.^{4, 7, 8, 9, 10}

This study was conducted to identify the prevalence of different rheumatic manifestations in

patients with hepatitis C in a tertiary care hospital in Pakistan.

Materials and Methods

Study was conducted at Rheumatology and Gastroenterology department of the Pakistan Institute of Medical Sciences, Islamabad, Pakistan. Inclusion criteria were (i) both male and female patients, (ii) age more than 16 years, (iii) presence of hepatitis C virus infection (diagnosed through presence of antibodies to hepatitis C virus and confirmed by positive PCR for hepatitis C virus RNA). Patients with (i) Hepatitis B virus Infection, (ii) already diagnosed to have HIV infection, (iii) previously diagnosed to have rheumatic disease and (iv) chronic illness (diabetes mellitus, chronic renal failure) were excluded from the study. Myalgias and arthralgias are a common side effect of interferon therapy so patients on current antiviral treatment were also excluded from the study. Although ongoing treatment with interferon was an exclusion criterion but patients who had a relapse of hepatitis C infection after receiving interferon and nonresponders were included.

Patients were evaluated by taking complete history, thorough physical examination followed by necessary investigations. They were inquired about the duration of hepatitis, presence of myalgias, arthralgias, arthritis, pattern of the joint involvement (mono, oligo or polyarticular), inflammatory or mechanical, duration of morning stiffness. History of Raynaud's phenomenon, rash on the body, paraesthesias of hand and feet, dryness of eyes and mouth was taken.

Patients were examined for the presence and pattern of arthritis, vasculitic rash, rheumatoid nodules, neuropathy and tender points. Laboratory work up included blood complete count, ESR and Liver function test. In Patients with arthritis, X- rays of the involved joint, rheumatoid factor and antiCCP antibody titers were done.

The data was analyzed through SPSS version 16 and various descriptive statistics were used to calculate frequencies, percentages, means and standard deviation. The numerical data (age, hemoglobin, erythrocyte sedimentation rate, ALT and viral load) was expressed as Mean $\pm$ Standard deviation. The categorical data (sex of the patient, duration of hepatitis, interferon therapy in past, presence of arthralgia, myalgia, fibromyalgia, arthritis, Raynauds phenomenon, paresthesia, numbness, vasculitis, dry eyes, dry mouth, neuropathy, early morning stiffness, presence of positive rheumatoid factor, antiCCP antibodies, and x ray findings) was expressed as frequency and percentages.

Results

This observational cross sectional study was conducted between August 2010 and May 2011. One hundred consecutive patients with hepatitis C infection were recruited. There were 37% (37) males and 63% (63)

females. Mean age was 41.39 ± 10.191 years (range 18 to 65 years). Non-responders to prior interferon therapy were 40 out of 100. Baseline characteristics of the patients are summarized in table I.

Table I. Baseline Characteristics of Patients (n = 100)

Characteristics	Value
Mean Age $\pm$ (SD), years	41.39 ± 10.191
Male /Female ratio	37/63
Duration of Hepatitis	
< 6 months	18
> 6 months	82
Interferon Therapy in past	40
Mean Hemoglobin g/dl $\pm$ SD	12.703 ± 2.1335
Mean ESR mmHg in 1 st hour $\pm$ SD	23.65 ± 13.648
Mean ALT IU/L $\pm$ SD	71.04 ± 66.259

SD=standard deviation, ESR=erythrocyte sedimentation rate, ALT= alanine amino transferase, IU= international unit.

Table II. Features of patients with arthritis (N=18)

Variable	Number	Percentage
Joints Involved		
Monoarthritis	2	11
Oligoarthritis	9	50
Polyarthritis	7	39
Duration of Arthritis		
< or = 6 weeks	2	11
> 6 weeks	16	89
Duration of EMS		
< 1 hour	12	89
≥ 1 hour	6	11
Subcutaneous Nodule	0	0
RA Factor		
Positive	7	39
Negative	11	61
Anti-CCP		
Positive	5	28
Negative	9	50
Not Done	4	22
X-Ray Findings		
No Abnormality	9	50
Periarticular	2	11
osteopenia		
Joint space narrowing	1	6
Erosions	1	11
Changes of OA	4	22

EMS= early morning stiffness, RA factor= rheumatoid factor, Anti CCP= anti cyclic- citrullinated peptide antibodies, OA= osteoarthritis.

Percentage of rheumatic manifestations

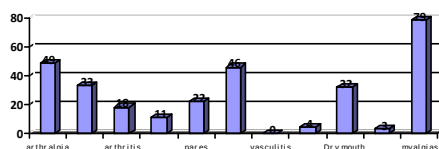


Figure 1. Arthralgia=49%, fibromyalgia=33%, arthritis=18%, Raynaud's Phenomenon=11%, paresthesia=22%, numbness=46%, vasculitis=0, dry eyes

A wide Spectrum of different rheumatic manifestations was found. Myalgias were the most common found in 79 patients followed by arthralgias in 49, fibromyalgia 33, Raynaud's phenomenon 11, paraesthesia 22, numbness 46, neuropathy 3, vasculitis 0, dry Eyes 4 and dry mouth in 32 patients. Percentages of different manifestations are illustrated in figure1.

In the analysis of a subgroup of the patients with arthritis 18% (N=18) it was found that 16 (88%) patients had arthritis of more than 6 weeks duration. Clinical and radiological evidence of osteoarthritis was found in 4 (22.2%) patients and all of them were more than 40 years of age. In these 4 patients with non inflammatory arthritis anti CCP antibodies were not checked.

Inflammatory arthritis was present in 14(14%) patients. Out of these 14 patients rheumatoid factor was positive in 7(50%) and anti CCP antibodies in 5(35%) patients. Anti CCP antibody titers in 5 patients were 1200, 200, 86, 9.3 and 7.7 IU/ml. Patients who had antiCCP antibodies present in high titers met the ARA criteria for rheumatoid arthritis. These 3 patients were considered to have rheumatoid arthritis concomitantly with Hepatitis C infection. Inflammatory polyarthritis with positive antiCCP antibodies in low titers was present in 2 patients. Important features of the patients with arthritis are summarized in table II.

Discussion

Rheumatological manifestations are frequently encountered during the course of hepatitis C infection. Studies have shown wide range of prevalence of various rheumatic manifestations.^{1, 11, 12} In one study musculoskeletal manifestation were present in 90.5% of HCV patients attending rheumatology clinic and 65.8 % patients members of HCV support associations. The members of HCV support association had arthralgias in 34.1%, arthritis 12.2%, sicca symptoms in 43.9% and Raynaud's phenomenon in 9.8% of patients.¹ On the other hand a recent study conducted in Egypt reported rheumatic manifestation associated with HCV infection to be present in 16.39% patients.¹¹ In this study arthralgias were present in 6.5%, fibromyalgia 1.9%, myalgia 1.3%, arthritis 0.7%, cryoglobulinemic vasculitis

in 0.7% of patients.¹¹ In a large prospective study of 1612 patients with chronic HCV infection, the MULTIVIRC group reported a 74% prevalence of extra hepatic manifestations.¹³ Examining 90 HCV positive patients, rheumatic manifestations were found in 31%, the most prevalent being arthralgias (9%), arthritis (4%), cryoglobulinemia (11%), sicca symptoms (8%), and myalgias (24%).¹⁴ The current research is a cross sectional study which reveals myalgias, arthralgias, fibromyalgia, arthritis, sicca syndrome, paresthesia and Raynaud's phenomenon to be associated with hepatitis C infection. None of the patient had systemic vasculitis.

Articular symptoms represent the common musculoskeletal complaint.^{1, 12, 15, 16, 17} HCV related arthropathy may present as mono, oligo or poly arthritis.^{1,6,7,8}

A study conducted in France reported arthritis in 42.8% and 12.2% of patients attending rheumatology clinic and members of HCV support associations respectively.¹ In our study arthritis was present in 18% of the patients. Out of these 18 patients, monoarthritis was present in 2(11%), oligoarthritis 9 (50%) and polyarthritis in 7 (39%) of the patients.

A significant number of hepatitis C patients have positive rheumatoid factor in their serum irrespective of the presence of articular symptoms. Inflammatory polyarthritis related to hepatitis C is difficult to distinguish from rheumatoid arthritis. Data has shown antiCCP antibodies as reliable marker to distinguish between the 2 entities.^{3, 18, 19} Michele Bombardiari et al reported absence of antiCCP antibodies in patients with HCV infection irrespective of articular symptoms.³ Mark H. also reported that antiCCP antibodies were not observed in patients with uncomplicated HCV infection.¹⁹

Another study conducted in Japan also reported absence of antiCCP antibodies in patients with hepatitis C infection; however 2 patients (2.7%) with Primary biliary cirrhosis and 6 patients (10.5%) with autoimmune hepatitis had anti-CCP antibodies.²⁰

In our study 18 patients had arthritis (4 patients had degenerative and 14 inflammatory arthritis). Positive rheumatoid factor was present in 39% (7) of patients and 5 patients had positive anti CCP antibodies. AntiCCP antibodies were present in high titers in 3 patients. Their clinical, laboratory and radiological parameters were enough to make a diagnosis of rheumatoid arthritis concomitantly with hepatitis C. HCV infection and rheumatoid arthritis can coexist.¹³ For treating such patients a step wise approach using non biological and biological DMARDs is appropriate.¹³

Review of literature has shown that antiCCP antibodies can be found in low titers in patients with hepatitis C.^{4,7,8,9, 19} Positivity of these antibodies in patients in HCV infection was found to be 5.7%, 4.2 %, 8.82% and 4.5% in different studies.^{4,7,8,9} In our study two patients with inflammatory arthritis had marginally elevated antiCCP antibody levels. In these patients ARA criteria for

rheumatoid arthritis was not met and these patients were labeled as HCV associated arthropathy.

The exact mechanism by which HCV infection trigger arthritis has not been determined. It may be a local inflammatory response to synovial tissue damage caused directly by viral invasion or indirectly by deposition of cryoglobulin-induced immune complexes in synovial fluid.¹⁵ Articular manifestation although common in HCV infection, severity of liver disease does not correlate with their presence or absence. Our study does not show any correlation of severity of liver disease to the presence of rheumatic manifestations. There were few limitations in our study. (1) Sample size was small, so the study results can not be generalized and (2) anti CCP antibodies were not checked in patients without articular symptoms, so the presence of these antibodies in this group of patients could not be determined.

Conclusion

HCV infected patients reported a wide variety of rheumatological manifestations. Myalgias, arthralgias, sicca symptom, fibromyalgia, arthritis and Raynaud's phenomenon were the predominant features. Rheumatoid arthritis can occur concomitantly with HCV infection and antiCCP antibodies are present in high titres in this subset of patients. These antibodies can occasionally be found in low titres patients of HCV infection with articular symptoms.

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