ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES AS A TOOL IN DIFFRENTIATING PATIENTS WITH RHEUMATOID ARTHRITIS FROM PATIENTS WITH CHRONIC HEPATITIS C INFECTION-ASSOCIATED POLYARTICULAR INVOLVEMENT

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ABSTRACT

Objective: *To assess the utility of anti-cyclic citrullinated peptide (anti-CCP) antibodies in distinguishing between patients with rheumatoid arthritis (RA) and patients with polyarticular involvement associated with chronic hepatitis C virus (HCV) infection.*

Methodology: *All the patients enrolled in this study were examined in the outpatient department of medicine unit at Lady Reading Hospital Peshawar from February to December 2010. Serum anti-CCP antibodies and rheumatoid factor (RF) were evaluated in 29 patients with RA, 13 patients with chronic HCV infection a associated with articular involvement and 35 patients with chronic HCV infection without any joint involvement.*

Results: *Anti-CCP antibodies were detected in18 of 29 (62.1%) patients with RA, 7 of 13(53.8%) patients having HCV with RA like arthropathy but not in a single patient with chronic HCV infection with no articular involvement. Conversely, RF was detected in 25 of 29 (86.2%) patients with RA, 9 of 13 (69.2%) patients with HCV-related RA like arthropathy and 8 of 31 (22.9%) patients with HCV infection without joint involvement.*

Conclusion: *This concludes that anti-CCP antibodies can be useful in discriminating patients with RA from patients with HCV-associated arthropathy.*

Key Words: *Anti-cyclic Citrullinated peptide antibodies (Anti-CCPantibodies), Rheumatoid Arthritis (RA),*

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INTRODUCTION

Most patients with chronic hepatitis C infection are asymptomatic.A number of patients will experience symptoms that are due to liver disease or extrahepatic manifestations of hepatitis C virus infection.Extrahepatitis manifestations are common features in patients with hepatitis C virus[1,2].Rheumatologic complications of HCV infection are common and include mixed cryoglobulimenia, vasculites, sjogrens syndrome, arthritis and fibromyalgia[3].

Articular involvement is a frequent complication and the clinical picture varies widely[4,5] It ranges from polyarthralgia to mono articular or oligoarticular intermittent arthritis and symmetric chronic polyarthritis. Monoarticular or oligoarticular involvement affect larger joints and is associated with mixed cryoglobulinemia whereas symmetric polyarthritis displays a rheumatic arthritis (RA) like clinical picture[4,5].

RA like HCV related arthropathy can be clinically indistinguishable from RA itself and most patients with RA like HCV related plyarthritis fulfill the american college of Rheumatology (ACR) criteria for RA[6,7]. So differentiating patients with HCV related symmetric polyarthritis from patients with RA represent both diagnostic and a therapeutic challenge.

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The classical clinical picture of RA is not helpful in differential diagnosis so other diagnostic tools such as serological abnormalities may help in the differentiating these disorders. The detection of classical IgM rheumatoid factor (RF) is of little utility as diagnostic tools because of high percentage of patients with chronic HCV display serum RF reactivity and frequency of RF increases in patients with articular involvement[5,6].

The current available test anti CCP2 for Anti cyclic citrullinated peptide antibodies has shows a high specificity for RA accompanied by a reasonable high sensitivity[8-10].

Anti CCP2 detection is a diagnostic tool for early RA and predications factor in terms of disease progression and radiological damage[11-14].

There is no study published locally to focus on the possible utility of anti ccp antibodies in differentially RA from HCV related arthropaty.

The aim of this study is to evaluate patients with chronic HCV infection whether anti CCP antibodies are useful in distinguishing patient with HCV related arthropathy and patients with RA.

METHODOLOGY

All the patients enrolled in this study were examined in the outpatient department of medicine unit at Lady Reading Hospital Peshawar from February to December 2010.

A total of 44 patients with HCV infection were included in the study. Mean age 59 years, range 37–79).Patients with chronic HCV infection were diagnosed on the basis of the presence of anti-HCV antibodies and confirmed by the detection of viral RNA in serum. All the patients were subjected to careful historical interview and rheumatologic examination. On the basis of the presence of HCV-related arthropathy we identify two groups of HCV patients: group 1, including patients with articular involvement similar to RA like pattern (13 patients) and group 2, comprising patients without articular involvement (31 patients).

To compare the prevalence of anti-CCP antibodies in HCV patients with that in patients affected by RA we enrolled 27 consecutive in-patients fulfilling the ACR criteria for R A.

Bleeding was performed after informed consent had been obtained; serum was recovered and stored for the investigations.

Anti-CCP antibodies were detected with commercial enzyme-linked immunosorbent assay kits. Anti-CCP antibodies were considered to be positive when the absorbance was higher than the cut-off of the kit (5 U/ml). RF was assayed with a quantitative immunonephelometry test. RF was considered to be positive when the concentration was higher than the cut-off value of the kit (15 IU/ml).

All serum samples with a high concentration of RF or anti-CCP antibodies were further quantified after further dilution.

RESULTS

The main clinical characteristics of RA and HCV patients are summarized in Table 1 and Table 2 respectively. All patients affected by RA received treatment with various disease-modifying antirheumatic drugs.

Thirteen patients with HCV infections presented with RA like pattern. It was characterized by a nonerosive symmetric polyarthritis that affected the small diarthrodial joints of the hands in about 9 patients while four patients were affected by diffuse polyarthralgia.

The prevalence of anti-CCP antibodies and RF in each group of patients is shown in Table 3. Eig`hteen patients with RA (62.1%) were positive for anti-CCP antibodies and 25 (86.2%) for RF.In patients with HCV presenting with RA like articular involvement RA factor was present in about 69.2% whereas antiCCP antibodies was present in about 53.8% patients. In patients having HCV with no articular involvement no patient was having antiCCP antibody whereas 22.9% of patients are RA factor positive.

Table 1: Clinical and Demographic Characteristics of Patients with RA and Patients having HCV with Articular Involvement

Variable	RA (n = 27)	HCV and polyarthritis (n = 13)
Age (years)	38.02 ± 7.72	39.4 ± 5.96
Disease duration (years), median (interquartile range)	10 (2.5–13.5)	0.5 (0.5–11)
ESR (mm/h)	76.45 ± 20.3	56.9 ± 6.4
CRP (mg/l)	24.3 ± 11.06	20.7 ± 6.9

Table 2: Clinical characteristics of patients with HCV

Variable	HCV without articular involvement (n = 31)	HCV with RA like articular involvement (n =13)
Age (years)	42.7 ± 8.45	39.4 ± 5.96
Polyarthritis, no. (%)	0 (0)	69.2%
Polyarthralgias, no. (%)	0 (0)	84.6%
Cryoglobulinemia, no. (%)	5 (16)	2 (25)
Transaminase U/L		
ALT	72.5 ± 22.7	63.5 ±14.9
AST	58.7 ± 11.02	62.5 ±7.96

Table 3: Prevalence of Anti-CCP Antibodies and RF in the Serum of Patients Enrolled in this Study

Variable	RA (*n*= 27)	HCV without articular involvement (n = 31)	HCV with RA like articular involvement (n=13)
Anti-CCP: no. (%)	18(69.2%)	0 (0)	7(53.8%)
RF: no. (%)	25(86.2%)	8(22.9%)	9(69.1%)

	HCV with RA like articular features	HCV without articular features
Anti CCP positive	7	0
Anti CCP negative	6	31

The sensitivity, specificity, positive predictive values and negative predictive value is 53.8%,100%,100% and 83.7% as calculated from table below.

DISCUSSION

Extra hepatic manifestations are frequently observed in patients with chronic HCV infection with prevalence of more that 74%[1]. In a prospective study on a large cohort of HCV patients, articular involvement represent the most common extra hepatic manifestation, nearly 20%,[15].

Two different clinical subsets of arthritis have mainly been described[5]. Monoarticular or oligarticular intermittent arthritis affect large and medium sized joints invariably associated with mixed cryglobulinemia[14,16] and polyarticular symmetrical arthritis closely resembles RA[4,6,17].

Differential diagnosis between HCV related polyarthritis and true RA is often very difficult because most patient with HCV related polyarthirits fulfill ACR criteria for RA[5,6] So other markers are needed for differential diagnosis.

In addition with classical clinical feature of the disease, serological abnormalities such as the presence of RF are useful in the diagnosis of RA and RF is included in the ACR criteria for RA. RF detection is not useful for HCV related arthropathy because it is often observed in sera of patients with HCV.

The classical IgM RA is present in 60% pf patients with HCV related arthropathy[6].

Even IgA RF failed to demonstrate any specificity for RA compared with HCV related arthropathy[18].

Anti keratin Antibodies (AKA) have been shown to be useful in distinguishing between, RA and HCV related arthropathy. Although it shows a high specificity and low sensitivity for RA[11] In addition, detection of AKA in laboratories is difficult to standardize and had limited clinical utility.

The limits displayed by AKA and anti filagrin[19] were overcome after the discovery of citrulline residues is the main antigen target of AKA and anti filaggim antibodies. The

development of immune enzymatic test using cyclic citrullinated peptide to detect anti CCP antibodies largely overcome the problem[20].

The currently available so called second generation test Anti ccp2 has shown a high specificity for RA accompanied by reasonable sensitivity[8,10].

It is diagnostic tool for early stages of disease and predictive factor both in term of disease progression and radiological damage[11-14].

In this study we demonstrated that anti CCP antibodies may help in differentiating patients with HCV related polyarthropathy form RA.In our study 13 patients having HCV with RA like arthropathy prevelance of antiCCP antibody in about 53.8% of patients.The results are compareable to study published earlier[21]. Not a single patient had anti CCP antibody in about 35 HCV patients with no articular involvement.In contrast anti CCP antibody was present in about 62.1% of patients with RA compareable to results obtained in recent studies[8,9].

Differentiating between patients with RA and those with HCV-related arthropathy has great relevance in clinical practice. In fact, in contrast with RA, RA-like HCV-related arthropathy usually shows a relatively benign course that is not associated with bony erosions and joint deformation[5,6,16]. Thus, management of HCV-related arthropathy usually does not require the use of heavy immunosuppressive treatment[5,22], which is associated with potential hepatotoxicity as demonstrated in patients with RA with concomitant chronic HCV infection[23]or may worsen the evolution of liver damage in HCV-affected patients. Thus, an early differential diagnosis could be of great importance in establishing the correct treatment to prevent joint erosions in patients with 'true' RA as well as chronic HCV infection and reducing the risk of immuno-suppressive therapy in patients with HCV-related arthropathy.

CONCLUSION

In this study we provide evidence that anti-CCP antibodies are absent from the serum of patients with chronic HCV infection with absent articular involvement. The high specificity and good sensitivity of anti-CCP antibodies for RA is confirmed. We try to establish that the demonstration of anti-CCP antibodies in patients with HCV-related RA-like arthropathy can be helpful in treatment and will be further decide the course of treatment.

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CONTRIBUTORS

IA conceived the idea and planned the study. AT, ZA , IA & AM did the data collection and analyzed the study. All the authors contributed significantly to the research that resulted in the submitted manuscript.