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RESEARCH ARTICLE

Prevalence of HCV infection among Patients with Inflammatory Polyarthritis Resistant to Conventional Therapy

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Abstract

Introduction
HCV-related arthritis can present with clinical manifestations simulating rheumatoid arthritis (RA). Thus, it may be difficult to distinguish HCV related arthritis from RA. RF is positive in 80% of patients with RA, but in HCV-related arthritis, this positivity is between 54% and 82%.
Objective
Recognition of HCV infection among patients with inflammatory RF positive polyarthritis poorly responding to conventional treatment**.**
Methods
150 patients were screened for HCV and anti CCP antibodies. Cases with positive serology for HCV were further evaluated by Real time Quantitative PCR.
Results
129 patients were positive for HCV (86%). 117 patients (78%) showed HCV and RF positivity with negative Anti CCP. 12 patients were positive only for RF (8%), 9 patients were positive for Anti CCP and RF but negative for HCV(6%), 12 patients were positive for all (8%).
Conclusion
Patients with atypical inflammatory polyarthropathy who are exposed to DMARDs according to symptomatic affection, RF positivity and radiological prove of arthritic activity, should gain our attention for the possibility of associated HCV especially when presented with elevated liver enzymes or unsatisfactory response to treatment.

INTRODUCTION

Chronic HCV (CHC) infection is a worldwide public health hazard, with more than 180 million people affected. The extrahepatic manifestations associated with HCV can be explained by viral induced auto immune mechanisms due to both hepato and lymphotropism leading to the development of various hepatic and extrahepatic immune system disorders ; the so-called HCV syndrome [1].

Many pro-inflammatory cytokines are activated in chronic HCV. It has been shown to induce IL-1β production and secretion which enhances the hepatocytes to produce several pro-inflammatory cytokines and chemokines, such as IL-6, IL-8, and macrophage inflammatory proteins (MIP-1α and MIP-1β) [2].

HCV non-structural proteins (NS3, NS4, NS5) stimulate kupffer cells (KCs) to produce tumor necrosis factor-α (TNF-α) and IL-1β [3].

HCV has been shown to activate toll-like receptors (TLRs), which are implicated in the production of pro-inflammatory cytokines in the cells of innate immunity. Specifically, HCV core protein and NS3 protein have been demonstrated to activate TLR2 which activate, in turn, NF-κB with subsequent transcription of inflammatory genes [4].

TLR4 and TLR8 stimulation by HCV core enhance microRNA-155 and TNF-α production in monocytes [5].
CHC infection has been associated with enhanced hepatic and systemic oxidative stress which are significantly linked to chronic inflammation [6].

Hepatitis C-related arthropathy is a common extrahepatic manifestation of HCV infection and one of the most common rheumatologic manifestations is Polyarthralgia [7].

Arthritic affection in CHC can occur due to a coexistent rheumatologic illness, arthritis due to mixed cryoglobulinemia, HCV-associated arthritis which is caused by (local inflammation or direct viral invasion of the synovium) and arthritis induced by antiviral therapy.

HCV Arthropathy is usually intermittent, mono or oligoarticular, non-destructive arthritis or occasionally symmetrical polyarthritis, nondeforming, and primarily affects the small joints, simulating rheumatoid arthritis but with minimal morning stiffness with no rheumatoid nodules. Cryoglobulinamic arthritis occurs in 10% to 30% of HCV-related arthritis mainly occurs in older patients with long history of chronic HCV, It is a monarticular or oligoarticular, nondeforming that usually affects medium or large joints; its course is intermittent and benign [8].

Rheumatoid factor (RF) is the autoantibody that was first found in rheumatoid arthritis and defined as an antibody against the Fc portion of IgG. RF and IgG form immune complexes which are responsible for the disease process. It predominantly encountered as IgM. There is an association between rheumatoid factor and more persistently active synovitis, more joint damage [9].

Due to HCV lymphotropism IgM (RF) production is enhanced so commonly associated with HCV in 54% to 82% of patients [9].

Anti cyclic citrullinated peptide antibodies (anti CCP) which are directed against peptides and proteins that are citrullinated in inflammation through deamination of arginine residues. One of its identified antigens is citrullinated filaggrin [10].

Anti CCP in rheumatoid arthritis have high sensitivity (75–80%) and specificity (96–98 %) and considered one of the most specific antibodies for the diagnosis of rheumatoid arthritis [11].

Some studies have shown that anti-CCP antibodies are present in 4.5% to 7% of patients with HCV related arthritis [12].

It is difficult to differentiate between HCV associated arthropathy and early rheumatoid arthritis when articular damage and deformities have not yet occurred. Anti keratin antibodies (AKA) have been investigated which is enhanced in rheumatoid arthritis more than HCV but now it is replaced with Anti CCP [13].

HCV-related arthritis can present with clinical manifestation simulating RA. Thus, it may be difficult to distinguish HCV related arthritis from RA. RF is positive in 80% of patients with RA, but in HCV-related arthritis, this positivity is between 54% and 82% [9].

RF is relatively nonspecific and may be present in several diseases. On the other hand, CCP antibodies are more specific for RA (96%-98%) and present in approximately 75 -80% of patients. A significant proportion of patients with this form of polyarthritis fulfill the American College of Rheumatology (ACR) criteria for RA, and the majority test positive for rheumatoid factor (RF). Therefore, because of the high prevalence of positive RF in patients with HCV-related arthropathy, this test cannot be used reliably to distinguish this condition from classic RA [14].

Aim of the work

Recognition of HCV infection among patients with inflammatory RF +ve polyarthritis poorly responding to conventional treatment.

METHODS

A- Patient selection

From February 2013 to February 2014, we analyzed the clinical and laboratory data of 150 patients referred from rheumatology clinic Zagazig university, presented with chronic inflammatory polyarthritis and positive for rheumatoid factor who are exposed to conventional therapy as NSAIDS or (DMARDs) as methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, or steroids.
They are presented for evaluation of raised liver enzymes or unresolving arthritis. All patients were counseled about the study and signed an informed consent.
Patients were included if they had started therapy based on presence of inflammatory polyarthritis more than 6 months involving more than 2 joints with constellation of radiological signs and RF positivity and diagnosed by the referring physician as highly suspicious RA, without satisfactory improvement.
Patients were excluded if they had a clearly defined RA or any inflammatory rheumatic disease.
A questionnaire regarding the medical history, medication history and family history were obtained, Clinical signs of arthritis and systemic affection were evaluated as follows: number of joints involved, symmetry, presence of morning stiffness, pain with movement, insidious or acute, duration of the illness, joint swelling/erythema, alopecia, oral ulcers, rashes, psoriasis, ocular erythema and pain, oral ulcers and Reynaud's phenomenon.

B- Laboratory Evaluation

Routine investigations

-Investigations included determination of CBC, erythrocyte sedimentation rate (ESR), serum C reactive protein (CRP), liver function tests as serum aminotransaminase, gammaglutamyl transferase, alkaline phosphatase, albumin.
-IgM RF, ANA and uric acid.
-Radiology of the affected joints.

Specific investigations

-Serum samples were screened for the presence of anti-HCV antibodies using a microplate ELISA. Cases with positive serology were further evaluated for HCV RNA by Real time Quantitative PCR (COBAS Ampliprep/Taqman HCV monitor, with detection limit 15 IU/ml; Roche Diagnostic Systems.
-HBsAg, positive cases were further evaluated for HBV DNA by Real time Quantitative PCR.
-Anti CCP level

Results

Patients' characteristics

150 patients who fulfilled the inclusion criteria, included 99 females (66%) and 51 males (34%). Their main age 42.2 ± 7 years old. The body mass index (BMI) 28.5±1.5kg/m2, the duration of their arthritic affection was 2.6±1.6 years. 80 patients (53%) experienced symmetrical polyarthritis affecting small joints as metacapophalangeal (MCP), proximal interphalangeal (PIP), metatarso phalangeal (MTP), shoulder, hip joints. 70 pateints (47%) showed oligoarthritic affection.

Radiological Signs as soft tissue swelling seen in 47 patients (31.3%), Juxta-articular osteopenia in 80 patients (53.3%), Bone erosion in 15 patients (10%), Joint deformity in 8 patients (5.4%).

Serum aminotransaminases levels were elevated in 100 patients (AST 50.2±13 IU/L, ALT 71±18 IU/L) and normal in 50 patients (AST 30.5± 8 IU/L, ALT 28±9 IU/L), serum albumin 4± 0.5gm/dl, alkaline phosphatase 114± 26.5IU/L.

The markers of inflammation were increased which included mean ESR 38.6±14 mm/1st hour, CRP 6.4±2.2g/L, mean value of uric acid was 7.1±1.5 mg/dl. As shown in **table 1**
All the patients were positive for RF. 121 patients were negative for ANA (80.7%), however 29 patients were positive (19.3%).

We investigated the presence of HCV and Anti CCP in these patients. 129 patients were positive for HCV (86%), 83 females (64.3%) and 46 males (35.7%) (p= 0.000, odds ratio for HCV for cohort sex; F=1.145, 95% CI: 0.870-1.5, M=0.736, 95% CI: 0.36-1.51), real time HCV PCR was applied for all of them and was positive, its mean value was 488.9 ± 27.5 (SE) KIU/l. the prevalence of HCV according to the age groups was shown in **table 2.**

HBsAg was positive only in 12 patients (8%), 8 females (67%) and 4 males (33%). 7 patients showed co-infection with HCV. None of them showed positivity of HBV DNA by quantitative PCR which could be explained by predominance of HCV in the co-infected subgroup. In the remaining 5 patients, 2 patients were negative for HBV viremia, and the other 3 patients showed mild viremia 1800 ± 420.5 IU/l.

Anti CCP was positive in 27 patients (18%) (18 F, 9 M) and negative in 123 patients (82%) (81 F, 42 M). It was more frequent in age group 41-45, 46-50 years which included 14 patients (52%). odds ratio for Anti CCP for cohort sex; F=0.988, 95% CI: 0.735-1.33, M=1.024.736, 95% CI: 0.569-1.84).

ANA titre was positive in 29 patients (19%); of them 26 patients have HCV (89.6%) (Odds ratio for ANA positivity with HCV 0.637, 95% CI: 0.21-1.93).

12 patients were positive only for RF (8%), 9 patients were positive for Anti CCP and RF but negative for HCV(6%), 117 patients were positive for HCV and RF but negative for Anti CCP (78%), 12 patients were positive for all (8%) i.e. HCV infection associated with rheumatoid arthritis as shown in **table 3, figure 1**
The presence of HCV was negatively correlated with Anti CCP (r= -0.475, p=0.000), RF was negatively correlated with Anti CCP (r= -0.197, p=0.016).

DISCUSSION

The consensus for intensive treatment to manage early inflammatory arthritis has been adopted recently with the disease modifying antirheumatic drugs (DMARDs) in patients highly suspected to develop persistent and erosive arthritis [15].

If classic rheumatoid arthritis is found at presentation, the intention to treat is obvious, but if the patient is referred very early, the diagnosis and prognostic evaluation often cannot be made accurately as joint involvement by HCV is accompanied by RF positivity and can easily be mistaken for RA, especially if transaminases are normal and hepatic manifestations of HCV are clinically silent until late in the course of the disease.

It is frequently noticed that rheumatologists start DMARDs early in patients with acute inflammatory oligo or polyarthritis with evidence of radiological activity and RF positivity to limit the progression of joint affection and future disability.
HBV and HCV can present with several rheumatic manifestations and may have a role in the etiopathogenesis of autoimmune disease [16].

Immunosuppressive drugs are commonly used in the management of rheumatic diseases were shown to induce viral reactivation in HBV- and HCV-positive patients and sometimes flares are asymptomatic. Several case reports have documented HBV reactivation in inactive HBV carriers treated with methotrexate [17] and biologic agents [18].

There is an increasing need to perform HCV serologic tests during investigation of rheumatic diseases on a routine bases especially with refractory disease or when abnormality of liver laboratory tests are encountered as elevated transaminases which could be due to reactivation of the virus or a drug complication.

Our study were conducted on 150 patients who were referred due to unsatisfactory clinical improvement while on conventional anti rheumatic agents or due to elevated liver enzymes. When they are examined, they did not show the characteristic deformities of rheumatoid arthritis. We investigated the prevalence of HCV and HBV infections which were surprisingly high; the incidence of HCV infection was 127 patients (84.7%) however, HBV was documented in 12 patients (8%).

A low incidence of past or active HCV among patients with rheumatoid arthritis was documented in previous studies which ranged from 0.65% in French study [19] to 3.4% in Brazilian study [20], 2% in Iranian study [21]. A turkish study, 2014 showed that HBsAg prevalence was 2.3% in RA patients, HCV prevalence was 1.1% [22].

A study was conducted in Egypt, 2011 revealed that the incidence of HCV among RA patients was 20%, of them 12.7% showed proven viremia [23]. This appears to be coincident with the prevalence of HCV among general population. In our study the association of HCV with RA was seen in 12 patients (8%).

In all previous studies RA is clearly diagnosed, but in this study 117 patients (78%) showed HCV and RF positivity with negative Anti CCP, clinically there were no characteristic joint deformities. Radiologically, 31 patients (26%) showed mild soft tissue swelling, 77 patients (66%) showed Juxta-articular osteopenia, 9 patients (8%) developed Bone erosion. PCR for HCV RNA was positive in all of them. It is important to say that this subgroup of patients with atypical inflammatory polyarthropathy who are exposed to DMARDs according to symptomatic affection, RF positivity and radiological prove of arthritic activity, should gain our attention for the possibility of associated HCV especially when presented with elevated liver enzymes or unsatisfactory response to treatment. Of course, this could influence the selection of drug therapy as most of the drugs given to patients with RA are hepatotoxic.

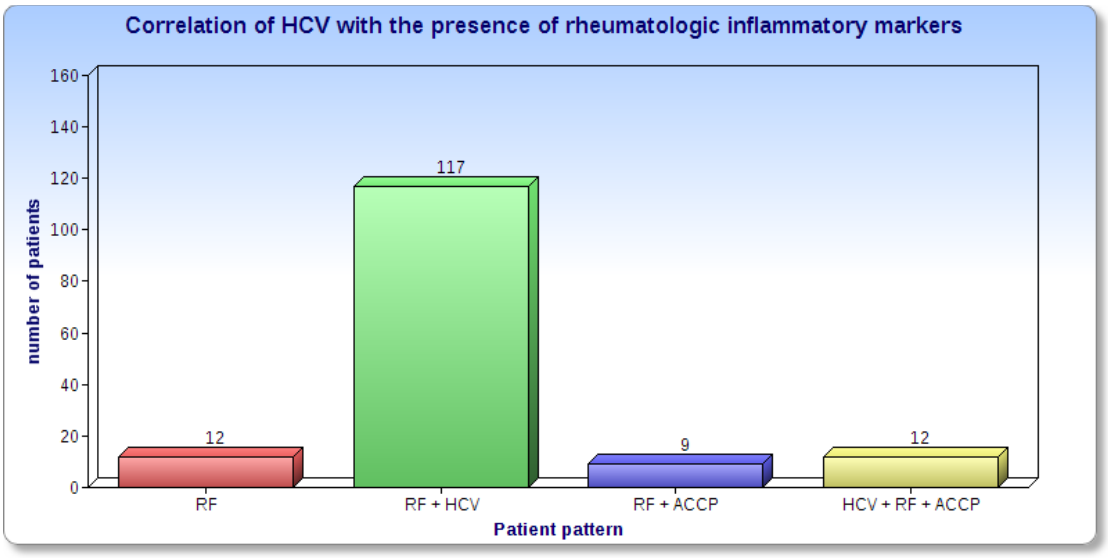
Abbreviations

ACCP: Anti cyclic citrulinated peptide
ACR: American college of rheumatology
BMI: Body mass index
CHC: chronic hepatitis C
DMARDs: disease modifying antirheumatic drugs
ELISA: enzyme-linked immunosorbent assay
ESR: Erythrocyte sedimentation rate
HCV: hepatitis C virus
KCs: Kupffer cells
KIU/L: Kilo international unit/liter
MCP: metacapophalangeal
MTP: metatarso phalangeal
NSAIDs: Non steroidal anti inflammatory drugs
NK-κβ: Nuclear factor - κβ
PASW: Prediction analytics software
PIP: Proximal interphalangeal
RA: Rheumatoid arthritis
RF: rheumatoid factor
SE: standard of error
TLRs: Toll like receptors

Competing interests

The authors declare that they have no competing interests.

Fig 1: Correlation of HCV with the presence of rheumatologic inflammatory markers



Variable	Patients (n= 150)
Age	**42.2 ± 7 years**
BMI	**28.5 ± 1.5 kg/m2**
Disease Duration	**2.6 ± 1.6 years**
ALT	**71± 18 IU/L**
AST	**50.2 ± 13 IU/L**
Albumin	**4 ± 0.5 g/dl**
CRP	**6.4±2.2 mg/L**
ESR	**38.6 ± 14 mm/ 1st hour**
Uric Acid	**7.1±1.5 mg/dl**
HCV-RNA KIU/mL	**420.74 ± 59.6 KIU/l**
Radiological Signs	
- soft tissue swelling	**47 patients (31.3%)**
- Juxta-articular osteopenia	**80 patients (53.3%)**
- Bone erosions	**15 patients (10%)**
- Joint deformity	**8 patients (5.4%)**

Table1: Demographic, laboratory and radiological characteristics of the study patients.

Age groups in years	30-35	36-40	41-45	46-50	51-55
HCV Patients (129)	30	20	38	26	15
Incidence of HCV	**23.2%**	**15.5%**	**29.5%**	**20.2%**	**11.6%**

Table 2: The Prevalence of HCV according to age groups.

No of patients	HCV Ab	RF	Anti CCP
12 (8%)	-ve	+ve	-ve
9 (6%)	-ve	+ve	+ve
117 (78%)	+ve	+ve	-ve
12 (8%)	+ve	+ve	+ve

Table 3: Correlation of HCV with the presence of rheumatologic inflammatory markers

References

1. Ferri C, Sebastiani M, Antonelli A, Colaci M, Manfredi A, Giuggioli D: Current treatment of hepatitis C-associated rheumatic diseases. Arthritis Res Ther 2012 Jun 25, 14(3):215.

2. Nishitsuji H, Funami K, Shimizu Y, Ujino S, Sugiyama K, Seya T: Hepatitis C virus infection induces inflammatory cytokines and chemokines mediated by the cross talk between hepatocytes and stellate cells. J Virol 2013 Jul, 87(14):8169-78.

3. Hosomura N, Kono H, Tsuchiya M, Ishii K, Ogiku M, Matsuda M: HCV-related proteins activate Kupffer cells isolated from human liver tissues. Dig Dis Sci 2011 Apr, 56(4):1057-64.

4. Dolganiuc A, Oak S, Kodys K, Golenbock DT, Finberg RW, Kurt-Jones E, Szabo G: Hepatitis C core and nonstructural 3 proteins trigger toll-like receptor 2-mediated pathways and inflammatory activation. Gastroenterology 2004 Nov, 127(5):1513-24.

5. Bala S, Tilahun Y, Taha O, Alao H, Kodys K, Catalano D, Szabo G: Increased microRNA-155 expression in the serum and peripheral monocytes in chronic HCV infection. J Transl Med 2012 Jul 30, 10:151.

6. Choi J, Forman HJ, Ou JH, Lai MM, Seronello S, Nandipati A: Redox modulation of the hepatitis C virus replication complex is calcium dependent. Free Radic Biol Med 2006, 41:1488–1498.

7. Rivera J, García-Monforte A, Pineda A, Millán Núñez-Cortés J: Arthritis in patients with chronic hepatitis C virus infection. J Rheumatol 1999, 26(2):420-424.

8. Nyingi M.K., Kenneth E. S: Hepatitis C-related arthropathy: Diagnostic and treatment consideration. J Musculoskelet Med Sep 2010, 27(9): 351–354.

9. Westwood OM, Nelson PN and Hay FC: Rheumatoid factors: what's new? Rheumatology Apr 2006, 45(4):379-85.

10. Sène D, Ghillani-Dalbin P, Limal N: Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjogren's syndrome. Ann Rheum Dis 2006, 65(3):394-397.

11. Raptopoulou A, Sidiropoulos P, Katsouraki M, Boumpas DT: Anti-citrulline antibodies in the diagnosis and prognosis of rheumatoid arthritis: evolving concepts. Crit Rev Clin Lab Sci 2007, 44 (4): 339–63.

12. Pinheiro GC, Scheinberg MA, Aparecida da Silva M, Maciel S: Anti-cyclic citrullinated peptide antibodies in advanced rheumatoid arthritis. Ann Intern Med 2003, 139(3):234-235.

13. Kessel A, Rosner I, Zuckerman E, Golan TD, Toubi E: Use of antikeratin antibodies to distinguish between rheumatoid arthritis and polyarthritis associated with hepatitis C infection. J Rheumatol 2000, 27610-612.

14. Nishimura K, Sugiyama D, Kogata Y: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med 2007, 146(11): 797-808.

15. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010, 69: 964–75.

16. Vassilopoulos D, Calabrese LH: Virally associated arthritis: clinical, epidemiologic and pathophysiologic considerations. Arthritis Res Ther, 2008, 10: 215.

17. Ostuni P, Botsios C, Punzi L, Sfriso P, Todesco S: Hepatitis B reactivation in a chronic hepatitis B surface antigen carrier with rheumatoid treated with infliximab and low dose methotrexate. Ann Rheum Dis 2003, 62: 686-7.
18. Esteve M, Saro C, Gonza´lez-Huix F, Suarez F, Forne´ M, Viver JM: Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. Gut 2004, 53: 1363-5.

19. Maillefert JF, Muller G, Falgarone G, BourJB, Ratovohery D, Dougados M, Tavernier C, Breban M: Prevalence of hepatitis C virus infection in patients with rheumatoid arthritis. Ann Rheum Dis 2002, 61:635–637.

20. Barbosa VS, Da Silva NA and Martins RM: Hepatitis C virus seroprevalence and genotypes in patients with diffuse connective tissue diseases and spondyloarthropathies. Brazilian Journal of Medical and Biological Research 2005, 38: 801-805.

21. Mohammad J E, Alireza R, Hamid MS, Negin S, Mohammad ME, Nahid M, Seyed JM, Mohammad Z: Frequency of hepatitis C in patients with rheumatoid arthritis. Iranian Journal of Clinical Infectious Diseases 2009; 4(1): 39-43.

22. Neslihan Y, Ömer K, Gezmiş K, Ayten Y, Sema Y, Umut K, Timuçin K, Hakan T, Birol B, Nurdan T: Prevalence of hepatitis B and C infections in rheumatoid arthritis and ankylosing spondylitis: A multicenter countrywide study. Eur J Rheumatol 2014, 1: 51-4.

23. Geilan A. Mahmoud A, Hania S, Zayed A, Mai M, Sherif B, Mervat M, Mostafa A : Characteristics of rheumatoid arthritis patients with concomitant hepatitis C virus infection. The Egyptian Rheumatologist 2011, 33:139–145.