

## Rheumatoid Case with HCV Infection

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**Case Presentation:** A 46-year-old woman referred to our center due to abnormality in aminotransferase level during check up. She had a history of blood transfusion 12 years ago. Anti-HCV Ab by ELISA method and HCV RNA by RT-PCR were positive. HCV RNA by Amplicor HCV monitor test counted 800,000 IU/ml and the genotype was 3a by Specific Primer-Targeted Region Core method. Laboratory evaluation revealed: Hb 11.9 mg/dl, WBC 5000 /ml, platelet count 190,000/ ml, ALT 70 IU/ml, AST 65 IU/ml, Alk phosphatase 210, PT 13 second, total protein 7.2 g/dl, albumin 4 g/dl, gama globulin 1.6 g/dl, HBsAg negative and RF positive. She had a history of symmetrical polyarthritis of small joints of upper extremities and morning stiffness for 3 years ago and had been managed as rheumatoid arthritis (RA) since then. She was managed with corticosteroids and methotrexate. Are there any relations between RA disease and HCV infection?

### HCV-related Arthritis

Rheumatologic complications of HCV infection are common and include mixed cryoglobulinemia, vasculitis, Sjogren's syndrome, arthritis and fibromyalgia<sup>(1, 2)</sup>. There is a well-defined picture of arthritis associated with the presence of mixed cryoglobulinemia that consists of an intermittent mono or oligoarticular, nondestructive arthritis affecting large and medium-size joints<sup>(1)</sup>. 2% to 20% of HCV-infected patients experience arthritis and as 50% experience arthralgia<sup>(3)</sup>.

### Clinical Manifestations

HCV-related arthritis (HCVra) commonly presents as rheumatoid-like, symmetrical inflammatory polyarthritis involving mainly small joints or less commonly as mono- or oligoarthritis of large joints. The joints involved in HCV-related arthritis are similar to RA<sup>(4)</sup>. In about two thirds of the affected individuals, morning stiffness may be severe, resolving after more than an hour<sup>(5)</sup>. Clinical picture of arthritis associated with the presence of mixed cryoglobulinemia in patients with HCV infection consists of an intermittent, mono or oligoarticular, nondestructive arthritis affecting large

and medium size joints<sup>(1)</sup>.

### What Are Differences Between True RA Disease and HCV-related Arthritis?

Differentiation between true RA and HCV-related arthritis may be difficult. HCV-related arthritis usually runs a relatively benign course that, in contrast to true RA, is typically nondeforming and is not associated with articular bony erosions<sup>(4)</sup>. Furthermore, unlike classic RA, ESR is elevated only in about half of the patients and subcutaneous nodules are absent<sup>(5)</sup>. Patients with HCV-related arthritis are seropositive for RF, but anti keratin antibodies (AKA) are a useful marker to differentiate patients with RA from these with HCV-related arthritis<sup>(6)</sup>. In a study AKA were detected in 69% of patients with RA compared to only 8% with HCV associated arthritis<sup>(6)</sup>. Positive HCV antibody and HCV RNA, and the absence of bony erosions, subcutaneous nodules may be useful in distinguishing between HCV-related arthritis and

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RA.

### Pathogenesis

Several pathogenetic mechanisms may be involved:

- 1- HCV arthritis may be a part of mixed cryoglobulinemia syndrome.
- 2- It may be directly or indirectly mediated by HCV infection.

Such possible, but yet not proven, mechanisms include direct invasion of synovial cells by the virus, eliciting local inflammatory response, cytokine-induced disease or immune complex disease, particularly in genetically susceptible individuals<sup>(5)</sup>. HLA-DR4 histocompatibility antigen is elevated significantly in HCV-infected patients with autoimmune diseases, including RA. In theory, patients who are genetically predisposed to autoimmunity develop polyarthritis consistent with a rheumatoid arthritis diagnosis<sup>(3)</sup>.

### Which Patients with Polyarthritis Should Be Tested for HCV Infection?

Risk factors for HCV infection such as transfusion and IV drug abuse or a history of hepatitis should be included in the history of present illness of any patient with polyarthritis<sup>(7)</sup>. In such patients serologic studies for hepatitis C should be performed<sup>(7)</sup>. Some authors recommend that any patient presenting with new onset of polyarthritis should be tested for HCV<sup>(3)</sup>. Furthermore, it is recommended to test for HCV infection in patients with Sjogren's syndrome and fibromyalgia<sup>(4, 5)</sup>.

### What Is the Best Treatment for HCV-related Arthritis?

The optimal treatment for HCV-related arthritis has not yet been established and a few data about HCVra treatment are reported in the literature<sup>(5)</sup>. Hydroxychloroquine, low doses of corticosteroids and NSAIDs are frequently administered to patients with HCV-related arthritis, but some authors describe an incomplete relief of symptoms, especially in the rheumatoid-like subset<sup>(9)</sup>. Intake of low doses of corticosteroids and NSAIDs is more effective in subjects belonging to the mono-oligoarthritis group<sup>(9)</sup>. On the other hand, Kessel *et al.* emphasized that HCV-related arthritis treated with steroids or cytotoxic agents can exacerbate HCV infection, and methotrexate or hepatotoxic drugs may negatively affect liver function<sup>(7)</sup>. Once

the diagnosis of HCVra is made, combination therapy with interferon alpha and ribavirin should be initiated. Use of antiviral drugs shows good results, but interferon alpha can worsen autoimmune disorders<sup>(9, 5)</sup>. Low dose oral corticosteroids, nonsteroidal anti-inflammatory drugs, hydroxychloroquine or sulfasalazine in addition to the antiviral therapy can be used to control arthritis-related symptoms<sup>(5)</sup>. Anti TNF therapy for RA in the setting of HCV appears to be safe and well tolerated without apparent influence on the underlying HCV infection; however, the usually non aggressive course of HCV-related arthritis does not justify their use as a current therapy<sup>(10, 11)</sup>.

### Recommendations

- 1- It may be recommended to test for HCV in any patient presenting with polyarthritis especially that high risk for HCV infection.
- 2- It may be suggested that combination of antiviral treatment with interferon alpha plus ribavirin should be initiated as a part of the therapeutic regimen in HCV-related arthritis. Low dose corticosteroids, NSAIDs or hydroxychloroquine can be added to antiviral drugs.

### Options in Future

Further research should be directed toward a better understanding of the pathogenesis of HCV-related arthritis. Also, additional research is needed to determine the optimal treatment of HCV-related arthritis and safety of IFN and anti-tumor agents in these patients.

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