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Rheumatoid Arthritis Induced by Interferon Therapy: A Rare Case Presentation

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Abstract

Introduction: *Interferon-α (IFN-α) is known for its antiviral and antiproliferative effects, used mainly for the treatment of chronic hepatitis C infection [1]. Immunomodulatory effects have been reported in patients treated with IFN-α, including hematological, immunological, rheumatological and dermatological disorders.*

Here by we report the case of a Caucasian woman who developed anticyclic citrullinated peptide antibody (anti-CCP)-positive RA following treatment of chronic hepatitis C infection with pegylated IFN-α2a.

Case Report: *A 57-year-old woman was diagnosed of chronic hepatitis C infection after detection of abnormal liver function. She was placed on a 24-week course of pegylated -IFN-α2a 180 µg weekly. After two months of antiviral treatment, she developed symmetrical polyarthritis, with pain and edema in the wrists, elbows, shoulders and metacarpophalangeal joints, associated with a prolonged morning stiffness. Ultrasonography of the hands revealed diffuse synovitis as well as tenosynovitis of the ulnar extensor tendons in both wrists. Anti-CCP was 41 IU/ml (negative < 20 IU/ml). A diagnosis of rheumatoid arthritis (RA) was made on the basis of clinical and ultra-sonographic data as well as Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity. Upon completion of a 12-week course of antiviral therapy, the rheumatoid syndrome disappeared after cessation of IFN therapy. By that time, antinuclear antibodies were in a titre of 1 /180, rheumatoid factor and Anti-CCP were negative.*

Conclusion: *This case shows that screening for RF and anti-CCP may be considered when treating with IFN, especially in presence of polyarthritis.*

Keywords: *rheumatoid arthritis, hepatitis C, Interferon-α, side effect, anti-CCP*

1. Introduction

Interferon-α (IFN-α) is known for its antiviral and antiproliferative effects, used mainly for the treatment of chronic hepatitis C infection [1]. Immunomodulatory effects have been reported in patients treated with IFN-α, including hematological, immunological, rheumatologic and dermatological disorders. In fact, IFN-α may lead to the induction or exacerbation of autoimmune diseases such as psoriasis, systemic lupus erythematosus, and rarely rheumatoid arthritis (RA).

We report the case of a Caucasian who developed anticyclic citrullinated peptide antibody (anti-CCP)-positive RA following treatment of chronic hepatitis C infection with pegylated IFN-α2a.

2. Case Report

A 57-year-old woman was diagnosed of a chronic hepatitis C infection after detection of abnormal liver function. She has a genotype Ib with a high viral load: RNA was 100,000 UI/ml. Liver histology showed advanced fibrosis and severe activity (A3 F4 according to metavir score). A history of blood transfusion was found. The patient was placed on a 24-week course of pegylated-IFN-α2a 180 µg weekly and a 1000 mg daily dose of ribavirin. After two months of antiviral treatment, she developed symmetrical polyarthritis, with pain and edema in the wrists, elbows, shoulders and metacarpophalangeal joints, associated with prolonged morning stiffness. The musculoskeletal examination was notable for active synovitis of the proximal phalangeal

joints, metacarpophalangeal joints, wrists, elbows. Distal interphalangeal joints were spared. She had no musculoskeletal symptoms prior to antiviral therapy. Review of systems was otherwise unremarkable. X-ray showed no remarkable findings. Ultrasonography of the hands revealed diffuse synovitis as well astenosynovitis of the ulnar extensor tendons in both wrists. Laboratory results revealed a normal C-reactive protein, elevated liver enzymes: ALAT (alanine-aminotransferase) 119, ASAT (aspartate-aminotransferase) 66, Gamma-GT 203 and undetectable cryoglobulins. Anti-CCP was 41IU/ml (negative <20 IU/ml), antinuclear antibodies were positive 1280 (negative<160), rheumatoid factor was 192 (normal < 30 IU/ml).

A diagnosis of rheumatoid arthritis (RA) was made on the basis of clinical and ultra-sonographic evidence as well as Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibody positivity. Moreover, an autoimmune thyroiditis was found that evolved into hypothyroidism treated with thyroxine.

The patient developed a sustained viral response as evidenced by persistent undetectable HCV RNA and normal aminotransferase activities. Upon completion of a 12-week course of antiviral therapy, the rheumatoid syndrome disappeared after cessation of IFN therapy. By that time, antinuclear antibodies were in a titre of 1 /180, rheumatoid factor and Anti-CCP were negative.

3. Discussion

HCV is the most common cause of cirrhosis and hepatocellular carcinoma (HCC). The combination of pegylated Interferon-alpha and ribavirin is the current standard of care to treat HCV infection [2]. Several side effects have been described with interferon therapy. Fatigue, fever and myalgia are the most common occurring in 40–55% of patients, while skin events have been reported in up to 20% [3]. Immune-mediated diseases have been frequently reported in patients with chronic HCV infection receiving IFN-α treatment such as hemolyticanemia, hypothyroidism, sarcoidosisand during the last years, rheumatoid arthritis is another reported side effect [3].In 1996, Okanoueet al reported that out of 677 patients treated with high-dose of Pegylated IFN for chronic hepatitis C infection, only 2 patients developed RA [4].Since then, RA episodes induced by IFN-α have rarely been reported [1].

HCV-related inflammatory arthritis has been described as falling into two subsets [1]. One subset is associated with mixed cryoglobulinemia and is usually monoarticular. The other subset is a symmetrical RA-like polyarthritis lacking juxta-articular erosions and rheumatoid nodules with positive RF. Patients affected with RA due to IFN-α should be distinguished from patients with HCV-related arthritis. The most relevant characteristic of HCV-related arthritis resides in the fact that it lacks anti-CCP titers and frequently improves after treatment with IFN-α, even without achieving a complete viral response, possibly as a consequence of decreased viral load [1]. Whereas, the arthritis in RA was described as persistent unresponsive to non-steroidal anti-inflammatory drugs and may require treatment with disease-modifying antirheumatic drugs if the symptoms do not resolve after discontinuing PEG-IFN.

Only 4 cases of RA associated with recombinant or IFN-α treatment for CHC have been previously reported in the literature [2]. The physiopathology associating pegylated-IFN and RA remains unclear because of the small number of cases reported. It has been reported that IFN-α determines a shift of T-lymphocyte responses towards a T-helper (Th)-1 profile, inhibiting the production of Interleukin (IL)-10 and stimulating the release of tumor necrosis factor (TNF)-α and IL-12 [2]. Another hypothesis is that BAFF induction, occurring during treatment with IFN-α, may favor the development of RA in susceptible individuals. In a case report, RA developed three months after cessation of antiviral treatment, while in the other reports RA occurred during treatment, with an interval ranging from 10 to 42 weeks of therapy [2]. In our case, the delay was 8 weeks. The temporal relation between the introduction of the drug further strengthens the case for a causal association and disease appearance, its remission with therapy cessation and the recurrence of symptoms on re-challenge.

4. Conclusion

In conclusion, we report a case of RA occurring during a course of PEG-IFN-α plus ribavirin for the treatment of hepatitis C. The present case suggests that biological agents, affecting the cytokine network, may work as triggering factors for the development of RA in previously predisposed individuals. Screening for RF and anti-CCP may be considered before treating with IFN. In addition, a close surveillance for

the occurrence of autoimmune phenomena during and after treatment should be worthy, for early diagnosis and adequate clinical management.

HIGHLIGHTS

- Immunomodulatory effects have been reported in patients treated with IFN-α and include rheumatological disorders.
- Screening for RF and anti-CCP may be considered before treating with IFN.
- A close surveillance for the occurrence of autoimmune phenomena during and after treatment should be worthy, for early diagnosis and adequate clinical management.

CONTRIBUTORSHIP

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST AND SOURCE OF FUNDING

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