Interferon-α induced psoriatic arthritis and autoimmune hemolytic anemia during chronic hepatitis C treatment

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ABSTRACT

Chronic hepatitis C (CHC) can occur simultaneously with a myriad of rheumatic diseases or can induce autoimmunity. Inflammatory arthropathy is the main extra-hepatic manifestation of infection by virus C. In addition, the treatment for CHC with INF-α and ribavirin is also able to cause some immune-mediated events. The present case report describes an unusual case of psoriatic arthritis (PsA) and autoimmune hemolytic anemia (AIHA) during therapy for CHC.

Keywords: Psoriatic arthritis; Chronic hepatitis c; Autoimmune hemolytic anemia; Treatment

INTRODUCTION

Chronic hepatitis C (CHC) can occur simultaneously with a myriad of rheumatic diseases, particularly rheumatoid arthritis (RA), Sjögren's syndrome and systemic lupus erythematosus (SLE). In addition, virus C can induce several immune-mediated events, such as non-erosive inflammatory polyarthritis, asymmetrical oligoarthritis and dermal vasculitis, usually secondary to mixed crioglobulinemia[1]. These clinical features may also derive from the treatment for CHC with interferon-alfa (INF-α) and ribavirin (RIBA)[2].

INF-α has antiviral, antiproliferative and immunomodulatory effects and has been used to treat multiple sclerosis, chronic myeloid leukemia, non-Hodgkin lymphoma, Kaposi's sarcoma and carcinoid syndrome. Nevertheless, therapy with INF-α has been associated with some adverse reactions, such as fever, chills, myalgia and polyarthritis, leucopenia and thrombocytopenia, increase in serum aminotransferases, cognitive and humor impairment and cardiac insufficiency. Although less frequent, exacerbation of pre-existing or induction of autoimmune disorders has been described, such as pernicious anemia, thyroid disorders, vitiligo, autoimmune hepatitis, diabetes mellitus, RA and SLE.

The prevalence of these events has been estimated at 20%, but it is difficult to know their real incidence, due to wide variety of autoimmune disorders that occur during infections by virus C[2,3,4]. It is interesting to note that in all cases described above there was a relevant participation of adaptive immune response, especially the Th2 pattern.

Case reports of exacerbation or de novo induction of diseases in which there is participation of innate immune response, such as spondyloarthritis, are rare. The present report describes an unusual case of psoriatic arthritis (PsA) and autoimmune hemolytic anemia (AIHA) during therapy for CHC in a previously healthy patient.

CASE REPORT

This report describes a case of a 54-year-old, white and cigarette smoking man carrier of hepatitis C virus genotype III. He had a pretreatment viral load superior to 1 million copies and a liver biopsy exhibiting 2-grade portal inflammation and activity. From May to August 2011, he received treatment with peg-interferon alfa-2a and RIBA. Nonetheless, these medications were withdrawn because he developed symmetrical polyarthritis involving small and large joints, asthenia, significant weight loss (25 kg), physical disability (functional class IV) and refractory anemia, requiring more than 15 blood transfusions. This condition was not resolved after taking non-steroidal anti-inflammatory drugs. Although INF-α and RIBA had been discontinued after 3 months, his CHC viral load became negative in September 2011.

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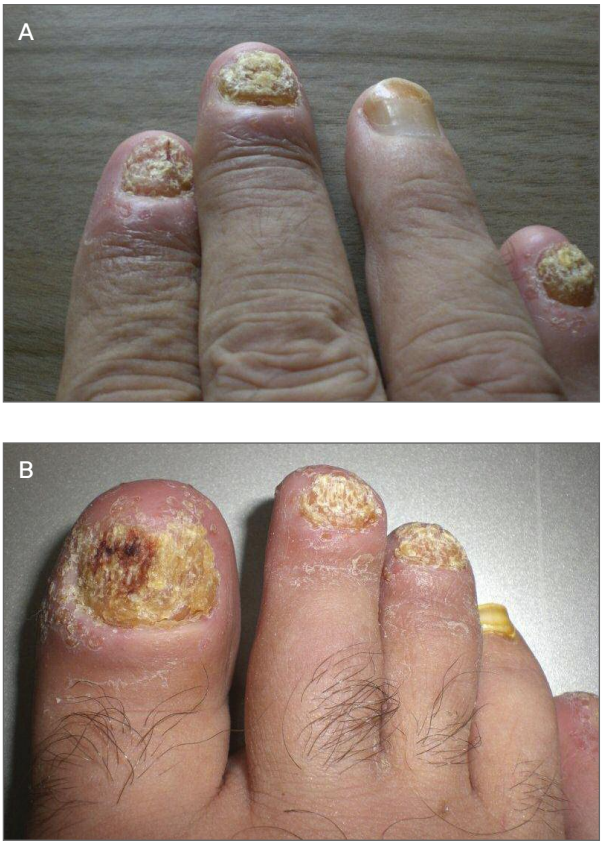

FIGURE 1. Marked nail distrophy of hands and feet. Swelling of toes

In October 2011, rituximab was prescribed due to persistent and refractory arthritis (rheumatoid arthritis sero-negative was diagnosed), but the patient had an anaphylactic reaction during its second infusion.

Four months after discontinuing INF-α and RIBA (December 2011), he presented whitish and desquamative lesions in some nails. The direct examination and cultures for yeasts were negative.

In April 2012, the patient showed synovitis in small joints of hands and feet, as well as in wrists, elbows, shoulders, knees, ankles and hips (DAS28=8.46; SDAI=84; CDAI=74). Besides, he has complained inflammatory back and neck pain (BASDAI=5,4). Detailed physical examination revealed onycholysis, leukonychia, subungual hyperkeratosis and thimble-like point depressions, featuring nail dystrophy in hands and feet related to nail psoriasis (Figure 1). In addition, he had already dactylitis in second right and fourth left toes.

Laboratory tests showed anemia (hemoglobin=8,7g/dl; hematocrit=28,3%; normal white blood cell and platelets counts) with reticulocytosis (22,5%),

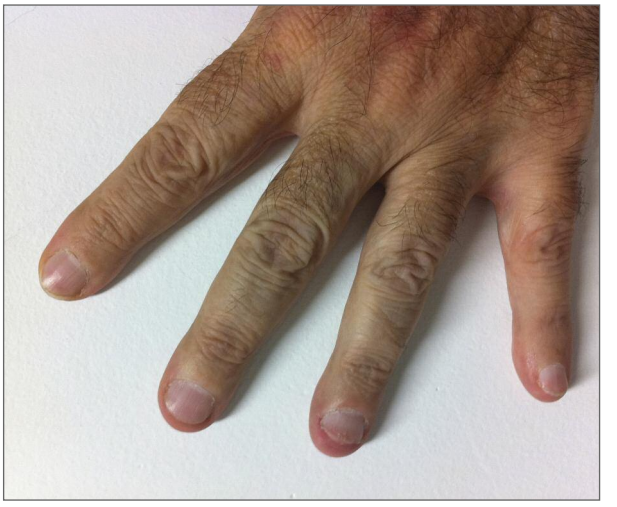

FIGURE 2. Improvement of nail distrophy after starting prednisolone therapy

elevated lactate dehydrogenase (1038U/L) and indirect bilirubin (1,9%mg/dl), positive direct Coombs test and bone marrow with granulocytic hypocellularity and red section hypercellularity, confirming AIHA diagnosis. Moreover, he had erythrocyte sedimentation rate of 120mm and C-reactive protein of 10.4mg/L and he was positive for HLA-B27. Rheumatoid factor, antinuclear antibodies (ANA), antibodies against extractable nuclear antigens (ENA) and anti-citrullinated protein antibodies (ACPA) were negative. There was left grade III sacroiliitis in the first radiographic evaluation.

There was significant improvement of anemia, polyarthritis and nail dystrophy (Figure 2) after starting prednisone 40mg/day, although he had difficulty in controlling glycemia and blood pressure. Due to poor control of AIHA, we decided for prescribing azathioprine and not cyclosporine as sparing steroids agent, combined to etanercept for adequate control of peripheral and axial joints complaints.

DISCUSSION

The main extra-hepatic manifestation of infection by virus C is joint involvement similarly to rheumatoid arthritis. On the other hand, features of PsA in CHC patients taking INF-α and RIBA are not common[1].

Although Taglione et al have showed higher virus C infection prevalence (12%) in 50 Italian patients with PsA[5], Palazzi *et al.* have not found difference in 100 PsA patients and 100 patients with osteoarthritis or

low back pain[6]. However, rare cases of PsA or psoriasis can occur after CHC treatment with INF-α[7-14].

Histologic examination of skin lesions and synovium of patients with PsA shows an inflammatory infiltrate composed mainly of CD4+ and CD8+ T lymphocytes, but also with participation of neutrophils, macrophages, dendritic cells, mastocytes and fibroblasts. In skin lesions, there is enhanced expression of genes related to the production of cytokines related to Th1 pattern, inducing IFN-γ, highlighting its relevant pathophysiological role. Furthermore, it induces expression of costimulatory molecules and TNF-α production by macrophages and monocytes, which amplify the inflammatory response[15].

Paradoxically, psoriasiform lesions may also appear after treatment with other immunomodulatory agents, especially TNF-blockers, in patients with chronic inflammatory arthritis. These lesions commonly appear 12 weeks after starting those medications and affect unusual regions such as the groin and pubic or palmoplantar area[16].

Nail dystrophy and symmetrical erosive arthritis affecting small and large joints during CHC treatment suggests that PsA has been triggered by IFN-α in a patient genetically predisposed for spondyloarthritis (SpA), even without personal or family history of psoriasis or some other rheumatic disease.

Although apparently asymptomatic before CHC treatment, the patient evaluated with inflammatory back pain and there was left grade III sacroiliitis in his first radiographic evaluation. This finding is very interesting because the patient had only some months of back pain. However, he had already advanced features of ankylosing spondylitis related to psoriatic arthritis. Two main reasons can be highlighted, such as very fast axial progression or oligosymptomatic axial findings before CHC treatment.

One of the most interesting aspects is the presence of HLA-B27 allele in this patient. While it may be associated with increased risk of developing SpA, including PsA, it plays a protective role and greater resistance against viral progression (hepatitis B and C and human immunodeficiency virus) and certain protozoa infections, such as Plasmodium falciparum[20]. Thus, it is worthy to note that the clearance of CHC load in only 3 months can be related to this mechanism. The concomitance between the protective role and hazardous aspects suggests a more pronounced inflammatory and immune response that may cause both clearance of various pathogens and autoimmunity. These aspects are related to antigen presentation properties and genetic predisposition of HLA alleles that contribute to the imbalance of innate immunity and tissue injury during some infections.

Initially, anemia was attributed to the RIBA, one of the most implicated drugs in pathogenesis of anemia during treatment of CHC, due to its increased oxidative stress in erythrocyte membrane, mitochondrial toxicity, or even because myelosuppression resulting from negative feedback on erythropoietin receptors[17]. Nevertheless, due to the refractoriness of anemia even after withdrawn of RIBA and IFN-α, other causes were investigated. The evidence of peripheral hemolysis associated with hypercellularity of red section in bone marrow as well as a positive Coombs test and the patient's excellent response to glucocorticosteroids confirms the hypothesis of AIHA, documenting another immune-mediated event in this case report.

The case described above is of great clinical importance, since it describes two immune-mediated phenomena in the same patient after CHC treatment with IFN-α. The humoral response, evidenced by AIHA, and the innate response, as PsA, are examples of these two mechanisms in a genetically predisposed patient. One hypothesis to explain the coexistence of these clinical findings is based on switching of Th1 vs. Th2 pattern response, provided by the IFN-α and RIBA[18-20].

Traditionally, inflammatory response in psoriasis plaque is initiated by activating of T cells. This phenomenon is also observed in the cell membranes of erythrocytes, but with subsequent polyclonal activation of B cells. Furthermore, it is described an imbalance between different IFN subtypes, with relative increase in IFN-γ and enhanced T cell activation. Other cytokine receptors, such as CXCR3, are also mentioned as having a relevant function in innate response. Recently, the role of IL-17 and IL-23 has been referred as another pathophysiological mechanism involved in both immune-mediated processes, emphasizing another pattern of immune response, the Th17. It is also known that chronic exposure to the C virus could be a relevant probability, which would act as an immunological trigger in a genetically predisposed patient.

On the other hand, this patient has some protective factors, such as HLA-B27 presence, considered a good prognostic factor in CHC[20], and smoking, an aspect negatively associated with PsA and psoriasis, especially in HLA-Cw[6] negative patients[21].

In conclusion, we reported an unusual case of 2 immunological diseases in a genetically predisposed pa-

tient that has evaluated with adequate control of anemia and nail psoriasis after taking prednisone, azathioprine, and etanercept.

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