

CASE REPORT**AN UNUSUAL SIDE EFFECT OF INTERFERON ALFA 2A: DIGITAL CLUBBING****Mohammad Tanveer Alam, Sabhita Shabir Sheikh, Sina Aziz*, Mohammad Masroor**

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Interferon Alfa has been widely used to treat chronic hepatitis C virus infection. In this report, we present a case series of two patients referred to Sarwar Zuberi Liver Centre, Civil Hospital Karachi, who suffered from chronic hepatitis C. After getting detailed clinical examination and baseline work up prior to starting treatment, these patients were offered therapy with usual recommended dose of 3 million units of alpha-interferon subcutaneously thrice weekly. Both these patients developed clubbing of fingers during the course of treatment, one developing it during the 2nd month while the other during the 4th month. It was of grade II in one patient and of grade III in another and was bilateral in both the cases. Clubbing was not presented prior to start of treatment and no other secondary cause of clubbing was found in any of the case. These patients were not on any other drug that is known to interfere with interferon or can be associated with clubbing. No national or international data regarding such unusual side effect is available. Whether this effect is idiosyncratic or dose related and whether it is reversible or not after completion of treatment is yet to be established.

Keywords: Interferon Alfa, Clubbing, Adverse effect

INTRODUCTION

Interferon-alpha is the mainstay of treatment for chronic hepatitis B and C.¹ Standard initial therapy for chronic hepatitis C infection is recombinant interferon alfa-2b at a dose of 3×10^6 units administered subcutaneously 3 times per week for 6 months.² Side effects to drug therapy including fever, headache, malaise, fatigue, myalgia, and arthralgia are common but usually mild and do not lead to discontinuation of drug. Some rare adverse effects affecting renal, cardiovascular, ophthalmic and neurological systems have also been reported in few patients. Clubbing was never demonstrated before, developing as a side effect of this drug. We report a case series of two patients suffering with chronic hepatitis C who were put on interferon treatment, both of which developed finger clubbing during the course of therapy.

Case-1

A 29 years old male, resident of interior Sindh, presented at Sarwar Zuberi Liver Centre, Civil Hospital Karachi with chronic hepatitis C infection for treatment. On initial visit, he has no comorbid and no clinical signs and symptoms of any other systemic illness other than chronic liver disease. He was anti HCV and HCV RNA by PCR positive, while HBsAg negative with deranged alanine transferase levels. After taking a detailed history, clinical examination and baseline laboratory workup, the patient was started on interferon treatment with routine dose of 3 mU subcutaneously thrice weekly. He was not taking any other drug apart from interferon Alfa. He developed the usual common side effects to the drug including fatigue, headache, and flu like symptoms, insomnia, impaired concentration

and alopecia. Along with these, after two months of therapy, he developed digital clubbing which was not present before the start of treatment. It was bilateral and of grade III. This patient was then evaluated clinically for the possible secondary causes of clubbing but none was found. This patient was continued with treatment for one year since HCV RNA by PCR remained positive after six months. Most of the initial common side effects subsided and the patient remained well during the course of treatment. This patient did not come for follow up after completion of therapy so reversibility of clubbing after drug stoppage could not be documented.

Case-2

A 60 years old male, resident of Karachi, also presenting at Sarwar Zuberi Liver Centre for treatment of hepatitis C. He was anti HCV and HCV RNA by PCR positive with elevated liver enzymes while HBsAg negative. He had previous history of rheumatoid arthritis. He was taking analgesics occasionally for his joint pain but was not on steroids or other immunomodulatory drugs. He was also put on interferon treatment in similar recommended doses, after baseline clinical examination and initial laboratory work up. At routine follow up during the treatment, he was noticed to develop finger clubbing during the fourth month. Clubbing was bilateral and of grade II in this patient. Clubbing was not documented on initial evaluation prior to therapy and no other secondary cause could be established in this patient. Unfortunately treatment was stopped after four months since this patient developed severe drug intolerance with development of alopecia, pruritis, anxiety, dyspepsia and anorexia, as well as his previous rheumatoid

arthritis worsened with severe pain in shoulder, upper arm and knee joints. His HCV RNA by PCR was negative after three months. This patient also not came for follow up after stopping the treatment so reversibility of clubbing could not be established.

DISCUSSION

About 170 million individuals can be found with chronic hepatitis C virus infection all over the world.³ In hepatitis infection, interferon therapy is regarded as a mainstay among all available therapeutic options.

Interferon is antiviral and immunomodulatory proteins, inhibiting synthesis of viral DNA and RNA, and enhance the expression of HLA class I antigens, allowing recognition of infected cells by cytotoxic T cells. The immunomodulatory effects of interferon include enhancement of both natural killer (NK) cells and cytotoxic T cell activity.¹

Side effects to interferon therapy are common; they are usually minor but are problematic for a significant proportion of patients. Most of the side effects can not be predicted, but are reversible.⁴

The common side effects include flu like symptoms, fatigue, headache, anorexia, depression, impaired concentration, psychiatric symptoms, alopecia, thyroid dysfunction and bone marrow suppression. Few uncommon drug reactions which have been reported are nephrotic syndrome, interstitial nephritis, retinal ischemia, retinal vein thrombosis, hearing loss, facial and oculomotor nerve palsies, aggravation of psoriasis, myocardial infarction, septal cardiomyopathy and severe depression of left ventricular systolic function.⁵ But little is known about the mechanisms of many of the side effects of interferon Alfa.⁶

No data is yet available in Pakistan or abroad on the occurrence of clubbing as a side effect to this treatment.

Clubbing refers to structural changes at the base of the nails that include softening of the nail bed and loss of the normal 150-degree angle between the nail and the cuticle. Cause is not known with certainty but disorder may reflect platelet clumping and local release of platelet derived growth factor at the nail bed.⁷ Clubbing may resolve with appropriate treatment of the underlying cause.

Clubbing may be familial, idiopathic but several secondary causes have been demonstrated including respiratory, cardiovascular, malignancies, infective endocarditis, inflammatory bowel disease and liver cirrhosis esp. primary biliary cirrhosis and

hepatopulmonary syndrome occurring as a complication of cirrhosis.^{8,9}

Two of our patients developed bilateral digital clubbing of grade II and III during treatment with interferon alpha. Since one patient developed clubbing during the 2nd month and another during the 4th month, and both patients received the standard dose of 3mU thrice weekly, it can not be established whether this effect is dose related or idiosyncratic. Close follow up of these patients is also need to establish whether it partially or completely resolve after stoppage of the drug.

One study found that the highest incidence of clubbing occurred in patients with chronic liver disease¹⁰; this effect can be due to the underlying liver disease. But since it was not present on initial examination, and HCV PCR by RNA became negative in both patients, indicating that underlying cirrhosis may have not worsened, this effect is probably due to the drug treatment. But further supporting data is yet awaited.

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