

## Raynaud's phenomenon and bilateral olecranon bursitis co-existing in a patient with chronic hepatitis B and D treated with pegylated interferon

Shafique Rehman Arain, Tahira Perveen Umer

### Abstract

Pegylated interferon remains the first line treatment for patients with hepatitis D virus and more than one year therapy may be necessary. Interferon  $\alpha$  has the most extensive clinical application and is used for the treatment of chronic hepatitis B and D virus as well as HCV infections. The attachment of polyethylene glycol to interferon increases its half-life. Treatment with peg interferon is associated with many troublesome and occasionally with serious or even life-threatening side effects. In this case report, we have described a patient with chronic hepatitis B and D, who developed Raynaud's phenomenon, ischaemic digital necrosis and bilateral olecranon bursitis during Pegylated interferon therapy. The patient underwent a very extensive workup in order to determine the underlying cause of his digital ischaemia and olecranon bursitis, which was finally determined to be secondary to the use of Pegylated interferon.

**Keywords:** Pegylated Interferon; digital ischaemia; necrosis; Raynaud's phenomenon; bursitis.

### Introduction

An estimated 15-20 million individuals with HBV worldwide are found infected with HDV.<sup>1</sup>

HBV infection is endemic in Pakistan. If not treated earlier, Hepatitis B and D virus infection may decrease expectancy and quality of life, also increase the chance of transmission and cost of serious complication. PEG-Interferon is the only drug effective against HDV.<sup>2</sup> More than 1 year of therapy may be necessary, as there may be some benefit from treatment prolongation.<sup>2</sup>

Side effects severity associated with IFN- $\alpha$  therapy are variable, depends on the dose, susceptibility of an individual and duration. Constitutional symptoms are commonly encountered side effects seen with IFN therapy. Fatigue, headache, and fever were each reported in about 50% to 60% of treated patients.<sup>3</sup>

.....  
Department of Rheumatology, Liaquat National Hospital and Medical College, Karachi, Pakistan.

**Correspondence:** Shafique Rehman Arain. Email: drshafiq123@gmail.com

Although rare, but life threatening side effects may also occur.

We describe the case report of a young male patient, who developed rheumatological side effects, Raynaud's phenomenon, digital ulcerations and bilateral Olecranon Bursitis during the Pegylated Interferon therapy for chronic Hepatitis B and Hepatitis D infections. In order to find the cause of his presenting symptoms extensive workup was done, which was finally determined to be secondary to the Pegylated interferon therapy.

Combined vascular events and bilateral olecranon bursitis simultaneously during IFN therapy have not been reported in the past.

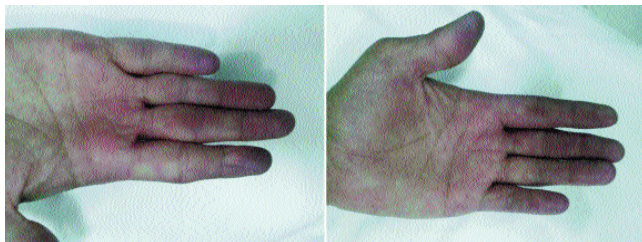
### Case Report

A 20 years old male from Balochistan, was diagnosed with Chronic Hepatitis B and D, six months back and started on Pegylated Interferon (Peg IFN) 180 mcg/week. He tolerated interferon therapy without major toxicity until 6th dose of Peg IFN, when he developed bluish discoloration of fingers of both hands, worsened by cold exposure. This, within 2 weeks progressed to painful ulcerations at the tip of all fingers. His symptoms improved when interferon therapy was stopped. He again developed same type of symptoms when Peg IFN was re-introduced.

After 2 weeks he also had occasional bilateral knee pain but no swelling or morning stiffness and noticed swelling behind both elbows, which were painful and red in colour. The pain was aggravated by movements. Later on, there was serous discharge from the swelling.

His symptoms improved when Interferon therapy was stopped. He again developed similar symptoms when Interferon therapy was reinstated after 2 months, but this time his symptoms were more severe in comparison to previous ones. His Interferon therapy was again interrupted and his symptoms improved. He developed all these symptoms three times during the course of Interferon therapy.

At the time when he attended the Rheumatology clinic, he was a thin lean boy. Both his hands showed bluish discoloration with digital ulcerations of 3rd, 4th and 5th



**Figure:**

fingers of the right hand. Both hands were cold with delayed capillary refilling. All the peripheral pulses were palpable and there was sensory loss. There was erythematous swelling at both elbow joints, about 2x2 cm in diameter with serous discharge, tender to touch. Rest of the Musculoskeletal and systemic examination was unremarkable.

Initial workup included CBC, ESR, CRP, Urea, Creatinine and electrolytes which were normal. SGPT 150 IU/L (n=<41 IU/L) in males and <31 IU/L in females), Alk Phosphatase 112 IU/L (n=<104 IU/L), Albumin 3.82 gm/dl (n=3.4 - 4.8 g/dl), PT 11/11 Sec, INR 1.0 (n=1.1), Uric Acid 4.3 mg/dl (n=<7.0 mg/dl in males, <5.7 mg/dl in females), HBsAg Reactive, Anti-HCV Non-Reactive, Anti-HDV Reactive, HBV-DNA by PCR Detected, HDV-RNA by PCR Detected. Ultrasound whole abdomen showed fatty Liver. Antinuclear antibody (ANA) was +homogenous. C3, C4, rheumatoid factor, anti-dsDNA, anti-smith, Anti-neutrophil cytoplasmic antibody, antitopoisomerase, anti-centromere, anti-Ro, anti-La, anti-RNP, anti-Jo1 and cryoglobulins all were negative.

Synovial fluid from right elbow: Smear showed light proteinaceous material with abundant Red Cells and few degenerated cells, protein 183mg%, cells 10/cmm, RBCs ++, Gram stain no organism seen, no monosodium urate crystals seen.

MRI both elbows without contrast showed findings consistent with bilateral Olecranon Bursitis with Inflammatory changes in surrounding soft tissue and Inflammation posterior to olecranon process on left elbow.

His Raynaud's phenomenon, digital ulcers and Olecranon Bursitis improved ONE month after discontinuation of Interferon therapy, intra-bursal Depomedrol injection and L/A of 2% GTN ointment.

So after a long discussion with gastroenterologist, his Interferon therapy had to be discontinued permanently.

## Discussion

Causes of digital ischaemic necrosis are most commonly

due to vasculitis, either autoimmune or drug-induced.<sup>4</sup>

Interferon  $\alpha$  has the most extensive clinical application and is currently primarily used for the treatments of chronic HBV and hepatitis D virus as well as acute and chronic HCV.<sup>5</sup>

Alpha interferons are type-1 interferons and are an important part of the innate antiviral immune response.<sup>6</sup>

Treatment with peg interferon is associated with many troublesome and occasionally with serious or even life-threatening side effects.

Ischaemia is a well-known complication of interferon- $\alpha$  therapy; ischaemic heart disease, ischaemic colitis, anterior ischaemic optic neuropathy, and Raynaud's syndrome with digital necrosis can all occur.

However, what is hardly known, especially in the literature, is that PEG-IFN therapy bears a risk of causing peripheral vascular toxicity with possible severe consequences. Rheumatological complications do occur with interferon therapy; however Raynaud's, and digital ulceration concomitantly with bursitis are not well established in the literature.

The underlying pathophysiological mechanism is obscure. The vascular profile as shown by angiography suggests endothelial proliferation consistent with vasculitis. Secondly, a direct vasospastic effect of IFN- $\alpha$  is also a possibility. Thirdly, in one case of IFN- $\alpha$ -associated Raynaud's syndrome histopathological examination of the arteries in an amputated finger showed multifocal arterial occlusion by thrombi.<sup>7</sup>

The exact cause of bursitis is also unknown. Different etiologies have been implicated such as, autoimmunity, infection and trauma.

Based on patients symptoms and extensive work-up, we concluded that the patient developed Raynaud's phenomenon, digital ulceration and bilateral olecranon bursitis as a result of treatment with Peg interferon  $\alpha$ .

There had been few case reports of vascular events which occur in patients treated with interferon  $\alpha$ . It has been suggested that peripheral vascular events, manifested by Raynaud's syndrome, occur more frequently during IFN- $\alpha$  than thus far known.<sup>8</sup>

It is possible however, that interferon related rheumatological complications are under-reported. Mostly, symptoms are moderate and consist of painful cyanotic fingers and intolerance to cold. However, the vascular complications can lead to atrophic acral lesions

or frank necrosis of digits.<sup>9</sup>

Symptoms and signs can be limited to one digit but in more severe cases more digits of both hands and feet are affected.

Al-Zahrani described a wide variety of vascular events associated with the use of interferon  $\alpha$ , including Raynaud's phenomenon, digital ulcerations and gangrene, pulmonary vasculitis and TTP/haemolytic uraemic syndrome (HUS).<sup>10</sup>

The median time from start of treatment to development of symptoms was 18 months (range 1-60 months).<sup>8</sup> Our patient developed these symptoms in 1½ months after IFN therapy, which were only limited to hands.

Treatment of Raynaud's phenomenon because of IFN therapy depends upon the severity of symptoms. Therapy with IFN has been continued without aggravation of symptoms in patients with mild attacks. In more severe cases, IFN- $\alpha$  was discontinued and treatment with vasodilators such as calcium antagonists or prostaglandins was initiated.<sup>11,12</sup>

We treated our patient in the same way.

These PEG-IFN related complications are considered clinically important because long-term interferon therapy is used in the treatment of various oncology and medical diseases.

## Conclusion

Peg IFN- $\alpha$  has various clinical applications and this is the only drug approved for the treatment of Hepatitis D.

Although rare, ischaemic digital necrosis, Raynaud's phenomenon and bursitis are potential adverse effects of Peg IFN therapy. Physicians in all areas of practice should be aware that Peg IFN may cause musculoskeletal side effects and substantially reduce overall quality of life.

## References

1. Abbas Z, Jafri W, Raza S. Hepatitis D: Scenario in the Asia-Pacific region. *World J Gastroenterol*. 2010; 16:554-62.
2. Castelnau C, Le Gal F, Ripault MP, Gordien E, Martinot-Peignoux M, Boyer N, et al. Efficacy of peginterferon alpha-2b in chronic hepatitis delta: relevance of quantitative RT-PCR for follow-up. *Hepatology*. 2006; 44:728-35.
3. Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. *Gastroenterology*. 2003; 124:1711-9.
4. Chen KR, Carlson JA. Clinical approach to cutaneous vasculitis. *Am J Clin Dermatol*. 2008; 9:71-92.
5. Feld JJ, Hoofnagle JH. Mechanism of action of interferon and ribavirin in treatment of hepatitis C. *Nature*. 2005; 436:967.
6. Borden EC, Sen GC, Uze G, Silverman RH, Ransohoff RM, Foster GR, et al. Interferons at age 50: past, current and future impact on biomedicine. *Nat Rev Drug Discov*. 2007; 6:975-90.
7. Liozon E, Delaire L, Lacroix P, Labrousse F, Ly K, Fauchais AL, et al. Syndrome de Raynaud compliqué de gangrene digitale au cours d'un traitement par l'interferon alpha. *Rev Med Interne*. 1997; 18:316-9.
8. Creutzig A, Caspary L, Freund M. The Raynaud phenomenon and interferon therapy. *Ann Intern Med*. 1996; 125:423.
9. Bachmeyer C, Farge D, Gluckman E, Miclea JM, Aractingi S. Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol*. 1996; 135:481-3.
10. Al-Zahrani H, Gupta V, Minden MD, Messner HA, Lipton JH. Vascular events associated with alpha interferon therapy. *Leuk Lymphoma*. 2003; 44:471-5.
11. Arslan M, Ozyilkan E, Kayhan B, Telatar H. Raynaud's phenomenon associated with alfa-interferon therapy. *J Intern Med*. 1994; 235:503.
12. Creutzig A, Freund M. Severe Raynaud's syndrome associated with interferon therapy. *Angiology*. 1996; 47:185-7.