

## Case Report

**Peg-Interferon Alfa 2-b Related Cellulitis in a 40 Years Man**Shahnaaz Sali<sup>1</sup>, Sahar Vakili Tabatabai<sup>1</sup>, Hooman Yousefi<sup>1\*</sup><sup>1</sup> Infectious Diseases and Tropical Medicine Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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**Abstract**

**Background:** Pegylated interferon and ribavirin are currently one of the accepted treatment for chronic Hepatitis C. Dermatologic complications of interferon have been reported, but to date a few cases of bacterial cellulitis; a rare and severe complication, have been published. Cellulitis is a common infectious process affecting the skin and subcutaneous tissues which results in significant morbidity and holds considerable healthcare costs.

**Cases Report:** Herein, we report a case of chronic hepatitis C genotype 1a who was on medication since 8 weeks prior to developing leg cellulitis, an uncommon pegylated interferon injection site. Considering no other possible risk factors were found to be in favor of bacterial cellulitis, our case is unique in its kind. Some reports reveal necrotizing vasculitis as basis for cutaneous lesions, which could be due to the high concentrations of drug at the injection site, a toxic effect of the diluents, or an immunological reaction.

**Conclusion:** According to the latter mechanism patients could develop bacterial cellulitis in their different organs. Conclusively, we propose the hypothesis of a possible association between cellulitis to occur at any site as the complication of pegylated interferon Alfa 2b and would highlight the role of a careful skin examination that could be an asset in preventing local skin infections.

**Keywords:** Hepatitis C, Pegylated interferon, Bacterial cellulitis

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**Introduction**

One of the current treatments for chronic hepatitis C is the combination of pegylated interferon and ribavirin. Previously, interferon was the only treatment, but the addition of a polyethylene-glycol side chain (pegylation) to the interferon gives it a much longer bioavailability, allowing for weekly injections rather than three injections per week<sup>1</sup>. When combined with pegylated interferon, ribavirin improves biochemical and virological response rates for most populations to 42 to 46 percent for patients with genotype 1<sup>1,2</sup> and 76 to 82 percent for patients

with genotypes 2 and 3<sup>2</sup>.

Pegylated interferon can cause wide range of complications such as neuropsychiatric emergencies, autoimmune reactions, ischemia, and infections including soft tissue problems<sup>3</sup>. Dermatologic complications of interferon Alfa have been reported, such as inflammatory reactions at the injection site, non-specific dermatitis and pruritis<sup>4-7</sup>. Although cases of cutaneous ulceration have been reported with pegylated interferon Alfa prescribed for melanoma<sup>8</sup>, few cases of bacterial cellulitis, a rare and severe complication of pegylated interferon Alfa, have been described as a consequence of subcutaneous

injections<sup>9</sup>. Hereby we report a case whose cellulitis was presented on his leg, not a common pegylated interferon injection site, considering no other possible risk factor found to be in favor of developing bacterial cellulitis.

## Case Report

A 40-year-old man, a shopkeeper, born and current resident of Tehran, Iran, presented to Labbafi-nejad Hospital, affiliated for Shahid Beheshti Medical University (SBMU), with an acute onset of edematous left lower extremity. He had suffered from leg tenderness and warmth since a week prior to admission, which gradually had got worse with no obvious abscess. He had some pruritic and painful lesions on the lateral side of his leg, and couldn't tolerate weight-bearing on his affected leg.

The patient had hepatitis C genotype 1a, which was due to his previous intravenous drug abuse, since 9 months ago and was under treatment with Pegylated interferon Alfa 2b peginteron:150µgr subcutaneously and ribavirin 600mg twice daily since 8 weeks ago. Furthermore, he denoted having car accident and a surgery on his affected leg 4 years ago, but did not mention any recent trauma to the affected leg. He didn't have any other significant past medical or familial history. He was neither diabetic nor Hepatitis B nor Human Immunodeficiency Virus (HIV) infected. He denied a history of insect bites, ingestion of medications, or other inter-current illness. The patient's complete immunizations had been received earlier. His habits consisted of occasional opioid consumption and smoking 20 pack-years.

During last 8 weeks, he reported having fevers or chills after injection of peginteron. Physical examination revealed an area of erythema, edema and warmth, sized 95mm x 80mm, with exudates. There was obvious tenderness on the site. Erythema encompassed the lateral side of his left leg. No fluctuations were detected. On initial exam, he was normo-tensive at 125/80 mmHg, heart rate at 72 beats/min, saturating 98% O<sub>2</sub>, and with a body temperature of 38.6°C. Arterial blood gasses demonstrated respiratory alkalosis.

His laboratory studies were significant for a normal white blood cell count of 4,800 cells per cu mm, without peripheral neutrophilia (54%), maybe due to

interferon he had relative leukopenia. The blood platelets count ( $126 \times 10^3/\mu\text{L}$ ) was low, erythrocyte sedimentation rate (ESR 31 mm/hr) was elevated and the C-reactive protein was 32mg/l. In addition, His blood and urine cultures had no growth. His leg wound cultures grew Gram Positive Cocci, staphylococcus aureus. Ultrasound scanning performed on the day following admission reported soft tissue edema and without collection, we planned to perform skin biopsy of affected skin but patient did not permit us.

Subsequently, the patient was admitted with presumed bacterial cellulitis and was treated with intravenously administered Vancomycin at 1 gram every 12 hours, and Clindamycin at 600 mg every 8 hours, for broad base coverage. His wounds were managed as per application of daily washing and clean dressing. The patient's cutaneous symptoms improved within 72 hours. IV antibiotic treatment was continued over 5 days, and was discharged on Ciprofloxacin, 500 mg twice daily and Clindamycin, 300mg thrice daily. The patient was successfully managed and he subsequently was followed up in the infectious disease clinic 1 week later without any signs of infection.

## Discussion

In some regimen Pegylated interferon is an essential component of the treatment in chronic hepatitis C virus (HCV) infection<sup>2</sup>. It comes in a pen injection system or a prefilled syringe<sup>10</sup>. Self-administering a subcutaneous injection can end in many intimidating consequences to some patients<sup>3</sup>.

Dermatologic complications of subcutaneous injections of interferon Alfa such as inflammatory reactions at the injection site, non-specific dermatitis and pruritis have been previously reported. A few cases of local cutaneous necrosis have also been described<sup>5,7</sup>. In randomized therapeutic trials of chronic hepatitis C comparing pegylated interferon Alfa 2a and interferon Alfa 2a for 48 weeks<sup>2</sup>, cutaneous side effects were found to be more frequent in the former. Bacterial cellulitis is a rare and severe complication of pegylated interferon Alfa<sup>9</sup>, which is a common infectious process affecting the skin and subcutaneous tissues. Along with other skin and soft tissue infections, it results in significant morbidity and holds considerable healthcare costs<sup>11</sup>. The incidence of lower-extremity cellulitis in Olmsted County

(Minnesota) was estimated at 199 per 100,000 person-years<sup>12</sup>. A recent study in Netherlands provided an incidence of about 2/1000/year when all forms of ‘cellulitis/erysipelas’ of the leg were taken together<sup>13</sup>. The Dutch study provided additional information: only 7% of the cases resulted in hospitalization, but these accounted for 83% of the total treatment costs. Not surprisingly the rate of hospital admission for ‘cellulitis/erysipelas’ increased sharply after 60 years of age to reach 1/1000/year in those aged above 75<sup>14</sup>.

At the present time, evidence-based clinical guidelines for diagnosis of cellulitis are lacking. Cellulitis is a clinical diagnosis and a potential medical emergency. Clinicians are given the challenging task of diagnosing a disease based on limited epidemiologic data and poorly characterized presenting symptoms<sup>15,16</sup>. As in our case, the diagnosis was made on clinical manifestation and ultrasound findings in respect of ethical rules.

Many side effects and drug interactions cannot be detected when drugs are approved. Yu et al<sup>17</sup> studied 617 treatment-naive Chronic Hepatitis C patients prescribed a 24-week protocol of peg-IFN/RBV, among which 29 (4.7%) patients terminated treatment early at <20 weeks. The reasons for early termination were flu-like symptoms/signs (n=9, 31.0%), irritability (n=1, 3.4%), severe urticaria (n=1, 3.4%), insomnia (n=2, 6.9%), pulmonary tuberculosis (n=1, 3.4%), suicide idea (n=2, 6.9%), poor response (n=2, 6.9%), depression (n=2, 6.9%), unwilling to continue (n=1, 3.4%), mortality (n=1, 3.4%), gastrointestinal upset (n=1, 3.4%), pancytopenia complicated with cellulitis (n=1, 3.4%), anaemia (n=3, 10.3%), overseas work (n=1, 3.4%) and an unknown cause (n=1, 3.4%).

Reported by El-Serag et al.<sup>18</sup> patients with HCV had a significantly higher prevalence of bacterial infection, including peritonitis, sepsis, endocarditis, cellulitis, and carbuncles in comparison with healthy controls.

Sixty-two (79%) HCV genotype 1 patients in a study by Howell et al.<sup>19</sup> completed 48 weeks of combination treatment with peginterferon Alfa-2a plus ribavirin. A case of cellulitis on day 493 (22 weeks after treatment was completed) was judged to be unrelated to treatment. These serious infections

were not associated with severe neutropenia or lymphocytopenia.

In the U.S. multicenter pilot study of daily consensus interferon plus ribavirin for “difficult to treat” HCV genotype 1 patients, Ho et al. investigated 64 patients with HCV genotype 1 to determine the efficacy and safety of daily pegylated interferon Alfa and ribavirin (RBV) for initial treatment. Overall early discontinuation of treatment before 24 weeks occurred in 34% of patients (9 due to intolerance; 10 due to noncompliance; 1 due to chest pain; and 2 due to cellulitis)<sup>20</sup>.

In a study by Suza et al<sup>21</sup> among 119 HCV patients treated with Interfrone and Ribavirin, 22 patients developed bacterial infections during or immediately after stopping therapy, 2 of which was diagnosed as cellulitis. Only 1 patient required hospital admission: a 72-year-old man with Child’s Class A cirrhosis developed cellulitis and edema of the lower extremities associated with high fever and prostration after 28 weeks of combination therapy. He required intravenous antibiotics, and both interferon and ribavirin were discontinued. He had not had significant neutropenia before therapy (1,670 cells /L) or while on therapy (mean neutrophil count was 1,118 cells/L) and recovered with treatment.

In a study of cellulitis among people who take peginterferon (peginterferon Alfa-2a; ribavirin) based on 8 reports from FDA and user community<sup>22</sup>, 991 people reported to have side effects when taking peginterferon. Among them, 8 people (0.81%) have Cellulitis. The time on peginterferon when people have cellulitis was mainly in 1 to 6 months and 2 to 5 years, similarly in our case the time between beginning of peginterferon and cellulitis presentation, 8 weeks, is in favor of causal association. Contradictly, most of patients taking peginterferon who have cellulitis were female (62.5% vs. 37.5%). Ages of people who have cellulitis were more than 40 years with a peak on 50-59 years. Top conditions involved for these people were hepatitis C and thrombocytopenia respectively<sup>22</sup>.

Fanny Lanternier et al. reported a case of 55 years diabetic man from Egypt with fever, chills and pain of the anterior left thigh five months after beginning of Pegylated interferon–Alfa 2b and Ribavirin for chronic Hepatitis C genotype 4 and a positive skin culture for

non-group able *Streptococcus* sp.<sup>23</sup>

## Conclusion

In our presented case cellulitis was not related to soft tissue infections of injection site, considering leg is not a common site for injection of pegylated interferon. Some pathologic reports reveal necrotizing vasculitis as basis for cutaneous lesions. It remains unclear whether vasculitis may be a result of the high concentrations of interferon at the injection site, of a toxic effect of the diluents, or of an immunological reaction<sup>9</sup>. According to the latter mechanism patients could develop bacterial cellulitis in their different organs. In conclusion, our case of leg bacterial cellulitis in a chronic HCV patient on pegylated interferon could propose the hypothesis of a possible association between cellulitis at any site as drug's complication and pegylated interferon Alfa 2b. Furthermore, the higher frequency of cutaneous side effects observed with pegylated interferon compared to classical interferon, a careful skin examination is recommended at all body sites in all patients, to prevent local skin infections such as cellulitis.

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