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Reactivation of Brucellosis during Pegylated Interferon-alpha therapy in a Thalassemic patient with Chronic Hepatitis C

Bita Behnava[1], Maryam Keshvari[2], Seyyed Mohammad Miri[1], Pegah Karimi Elizee[1], Seyed-Moayed Alavian[1]

[1] Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Tehran, Iran
[2] Blood Transfusion Research Center, Tehran, Iran

Summary

Interferon, as an immunomodulatory agent, may be responsible for reactivation of Brucellosis in immunocompromised patients such as subjects with thalassemia. We report a case of 52 year old man with brucellosis reactivation during the therapy with Pegylated Interferon-alpha for chronic HCV infection. History included: previous living in rural area, tangent with sheep and cattle, prolonged fever and night sweats. At 16 weeks of treatment patient was negative for HCV-RNA PCR but experienced flu-like syndrome. Afterwards, weight loss and positive serologic studies for brucellosis were present. Antibiotic therapy leaded to a good clinical response within a few days and for the six months later. In endemic region, the past history of brucellosis should be considered prior to start of Interferon-alpha therapy particularly in the immunocompromised hosts.

Key words: **Brucellosis • Hepatitis C • Thalassemia • reactivation • Interferon**

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Author's address: Seyed-Moayed Alavian, Baqiyatallah Research Center for Gastroenterology and Liver Diseases, Grand floor of Baqiyatallah Hospital, Mollasadra Ave., Vanak Sq., P.O.Box 14155-3651, Tehran, Iran; e-mail: alavian@thc.ir

Background

Brucellosis as a zoonotic infection worldwide can affect healthy individuals and immunocompromised patients living in countries that are endemic for the infection such as the Middle East countries and Iran [1,2]. Brucellosis can be transmitted to humans through contact with animals or their products; it is an occupational hazard to persons engaged in certain professions (e.g., veterinarians, slaughterhouse workers, and farmers) [2]. Both direct and indirect transmission such as consumption of unpasteurized milk and dairy products, herding, and lambing have been shown to have significant correlation with this disease [3].

On the other hand, hepatitis C infection as the most relevant causes of cirrhosis and hepatocellular carcinoma can be seen in patients who need recurrent blood transfusion through their life such as thalassemic patients [4,5]. The treatment of patients with HCV has improved steadily during the last decade, and the subcutaneous administration of Pegylated Interferon Alfa combined with oral Ribavirin, the current standard of care, has yielded response rates of more than 50%. However, monotherapy with Pegylated Interferon alpha, as the standard treatment in thalassemic patients with HCV, is compromised with a wide range of side effects such as some bacterial infections. These include neutropenia induced by bone marrow suppression, which is the most common reason for dose reduction and early drug discontinuation, and infection, which is the most prevalent severe adverse event in randomized clinical trials of Peginterferon and Ribavirin [6,7].

There are several reports of relapse of brucellosis in cell-mediated immunodeficiency states such as hematologic malignancies or Infliximab therapy [8,9]. This appears to be the first case of reactivation of brucellosis, occurred during the use of Pegylated Interferon-alpha.

Case Report

A 52-year-old man with major thalassemia was referred for hepatitis C infection, diagnosed 11 years ago. He received blood transfusions monthly until seven years ago, when he underwent splenectomy following treatment with Hydroxyurea. Patient had been living in a rural area in the east of Iran until 20 years ago and later on he immigrated to Mashhad (a city in northeast of Iran). In past he had a history of consumption of unpasteurized milk and cheese and also had contacts with sheep and cattle infected with brucellosis. In addition, his mother had a history of brucellosis 20 years ago and simultaneously, a patient had a prolonged fever and night sweats that had been treated with streptomycin and tetracycline for two weeks. He denied a consumption of unpasteurized dairy products or travelling to rural area for the last 7 years ago. Laboratory findings included: baseline HCV RNA: 564000 IU/ml (Amplicor monitor test) with genotype 1a; HBsAg: negative, HIV antibody: negative, AST: 125 U/L; ALT: 63 U/L; Alkaline Phosphates: 373 U/L; LDH: 1623 U/L; Albumin: 3 g/dl; WBC: 2400/µl with 52% Neutrophil, 47% Lymphocyte; Hemoglobin (Hgb): 8.8 g/dl; platelets: 391000 /µl and Prothrombin time: 18.8 seconds (control: 13 sec). Sonographic findings were coarse hepatic echo texture and nodularity with dilated portal vein (17 millimeter). Upper gastrointestinal endoscopy was normal. Treatment with pegylated interferon alpha-2a (Pegasys) was started at 180 microgram per week. The patient experienced mild fever and myalgia during the first week of treatment. Biochemical tests were assessed every four weeks besides hemoglobin every two weeks during treatment. After therapy, hemoglobin dropped below 8 g/dl and the patient required blood transfusion every three weeks. Quantitative HCV RNA PCR became negative on twelfth weeks of therapy. After 16 week of treatment, the patient experienced fever, fatigue, night sweat and back pain for 20 days. He treated himself with acetaminophen alone. In physical examination he had tenderness on sacroiliac joint but did not have any tenderness on lumbosacral spines. He had lost five kilogram of body weight. Secondary laboratory tests showed: WBC: 2990/µl with 53% neutrophil, 46% lymphocyte, 2% monocyte, Hgb: 8.9 g/dl, platelets: 210000/µl, ESR: 32 mm/h, AST: 65 U/L, ALT: 57 U/L, LDH: 950 U/L, Total bilirubin: 6.7 mg/dl, direct bilirubin: 2.5 mg/dl, prothrombin time: 18 second (control: 13 sec.). Serologic studies for brucellosis showed a positive tube agglutination test, anti-brucella titers: 1/640 and a positive 2-ME test, anti-brucella titer: 1/320. Treatment with doxycycline 100 mg twice daily and co-trimoxasole twice daily was performed for the first three weeks, followed by rifampin 600 mg/day and doxycycline at 100 mg twice daily for nine weeks. The patient had a good clinical response and became afebrile in a few days. Since, then he has remained stable with no signs of relapse of brucellosis after six months. Peginterferon therapy was discontinued after two weeks.

Discussion

We report a case of brucellosis during Pegasys therapy in a thalassemic patient with chronic HCV. The patient had lived in a hyperendemic area for brucellosis until 20 years ago and was tangent with source of infection. At that time he had a history of brucellosis that had been treated only for two weeks. He has not consumed unpasteurized dairy products or travelled to rural area for the last 7 years. According to previous exposure to brucellosis seven years before and a history of incomplete antibiotic therapy, it seems that he experience reactivation of past infection instead of a new infection.

Two studies in Iran showed that consumption of unpasteurized dietary products, existence of another case of brucellosis in the home and contact with infected cattle were the most important risk factors for infection [2,10,11]. Consumption of fresh cheese (22.4%), animal husbandry (11.3%), working in a laboratory (8.1%), and veterinary profession (1.5%) were the main risk factors for brucellosis infection in Iran [12,13]. Up to 10% of the patients relapse even after combination therapy [3]. Relapse may occur due to intracellular localization of the organism or inadequate treatment [14]. Patients with brucellosis have been treated with a variety of antibiotic regimens that may include doxycyline, tetracyline, streptomycin, rifampicin and others. Combination of tetracycline for six weeks plus streptomycin for the first three weeks is the most effective treatment [15,16]. A shorter duration of therapy is associated with a dramatically high rate of relapse or treatment failure [17]. Brucella is a facultative intracellular pathogen which can survive inside the host phagocytes and relapse several months or years later especially after an inadequate antibiotic therapy. The clearance

of Brucella depends on the activation of macrophages via adequate T-Helper 1 immune response [14].

Therefore, we thing, that a relapse of brucellosis has occurred in our thalassemia major patient with possible cirrhosis (sonographic findings and prolonged PT) during pegylated interferon alpha therapy. We conclude that reactivation of brucellosis in the present case, might be due to pegylated Interferon alpha, underlying diseases or synergistic effects of them. Major thalassemia is associated with a wide spectrum of immune abnormalities that were identified due to iron overload, multiple transfusions, zinc deficiency, or splenectomy [18,19]. Liver damage is aggravated by iron overload in thalassemic patients with chronic HCV [19,20]. However major thalassemia was not described as a risk factor for reactivation of brucellosis. Patients with cirrhosis have defects in both humeral and cell-mediated immunity. The present case probably has end stage liver disease. Although, like other intracellular opportunistic organisms, several cases of reactivation of brucellosis have been reported due to cell mediated immunodeficiency following HIV infection, hematologic malignancies, use of Corticosteroids and Infliximab [8,9,14], there is no reports of reactivation of brucellosis related to the use of Interferon alpha. Interferon alpha is an immunomodulatory agent and it can cause neutropenia due to bone marrow suppression and prone patients to some bacterial infections [6]. There has not been any hypothesis about iatrogenic suppression of cell mediated immunity by Interferon-alpha. Although, declines in CD4 counts and several opportunistic infections have been reported in HIV and HCV co-infected patients during Interferon-alpha therapy [21], but a severe cell mediated immunodeficiency state has not been described in none HIV chronic HCV patients treated with Interferon-alpha until now. Nevertheless, there have been several cases of reactivation of tuberculosis during treatment with Interferon-alpha for chronic hepatitis [22–24]. Most of them had underlying disease such as chronic renal failure and HIV infection or had a history of previous tuberculosis. In addition, Interferon-alpha may alter the regulation of cytokines network and predispose patient to some infections [22,23].

As a result, although Interferon-alpha has not been described as an immunosuppressive agent, it may be a facilitating factor for reactivation of opportunistic infections especially in immunocompromised hosts such as cirrhotic or HIV infected patients. It may be suggested that, in a region endemic for brucellosis, the past history of this infection should be considered prior starting of Interferon-alpha particularly in the immunocompromised hosts. Additionally, fever, night sweat and arthralgia in a patient on Interferon-alpha therapy should not be explained by side effects of Interferon-alpha and the probability of infections should be evaluated.

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