CASE REPORT

Unique side effects of interferon

Hina Aslam, Rashid Qadeer, Syed Mohammad Kashif, Muhammad Rehan, Salahuddin Afsar

Abstract

Interferon-alpha, a potent mediator of host immune response, has immunomodulatory properties in addition to its antiviral effects. A wide spectrum of autoimmune diseases can occur in patients treated with interferon-alpha for chronic hepatitis B and D, of which clinical systemic lupus erythematosus (SLE) accounts for less than 1% and hypothyroidism for 2-4 %. We report herein a case of a 16-year-old male who developed antinuclear antibody (ANA)-negative SLE and hypothyroidism after treatment with interferon-alpha for chronic hepatitis. High index of suspicion is therefore necessary in all patients treated with interferon for early diagnosis and treatment.

Keywords: Systemic lupus erythematosus, Hypothyroidism, Interferons, Hepatitis B, Hepatitis D.

Introduction

Increasing use of interferon alpha (IF-alpha), especially for chronic hepatitis, has drawn attention to the induction of various autoimmune phenomena.[1] Systemic lupus erythematosus (SLE), a chronic inflammatory disease of autoimmune origin, has been seen to develop after IF-alpha use. Rarity and unusual presentation of this disease in males can lead to unnecessary delay in its diagnosis.[2] Herein we report a patient whose male gender, young age, unusual presentation and negative antinuclear antibody (ANA) test created some diagnostic difficulties. However, a clue related to prior treatment with IF-alpha helped us to reach the diagnosis.

Case Report

A 16-year-old male presented to us in July 2014 with a 2-month history of fever, cough and pleuritic chest pain. He was previously treated with a 48-week course of interferon (IF)-alpha for chronic hepatitis B and D 6 years back. On presentation, he was very short of breath and had swelling on both feet. On the 3rd post-admission day he developed haemoptysis. On systemic inquiry, he complained of constipation. The patient did not have any family history of autoimmune diseases, but he had strong family history of tuberculosis (TB) and hepatitis B. He had never smoked. On examination, he was tachypnoeic with irregular pulse, had raised jugular venous pressure (JVP), an enlarged thyroid and pedal oedema. Swelling and tenderness of multiple small and large joints of body were noted. He had hepatosplenomegaly along with shifting dullness. Examination of the respiratory system revealed findings of pleural effusion on both sides. Initial laboratory investigations revealed haemoglobin of 9.2 g/dL (normal range: 13-17), mean corpuscular volume (MCV) 93.2 fL (80-96), total lymphocyte count (TLC)1037/mm^3, erythrocyte sedimentation rate (ESR) 122 mm/hr (0-22), serum creatinine1.7 mg/dL (0.6-1.2) which rose to 2.9 mg/dL on 3rd day, alanine aminotransferase (ALT) 544 U/L (10-40), total proteins 9.8 g/dL (6.0-8.0), serum globulin 7.7 g/dL (2.3-3.5) and albumin 2.1 g/dL (3.5-5.0). Coagulation profile was deranged with prothrombin time (PT) 18 seconds (9.5-13.5), activated partial thromboplastin time 30.6 seconds (30-40), and international normalised ratio (INR) 1.71 (0.8-1.2). Protein traces were seen on urine detailed report. Serology was negative for hepatitis C and human immunodeficiency virus (HIV) but positive for hepatitis B. His hepatitis B virus deoxyribonucleic acid polymerase chain reaction (DNA PCR) was done which was negative.

Thyroid profile showed primary hypothyroidism. Echocardiography showed thickened pericardium, septal bounce and pericardial effusion findings suggestive of effuso-constrictive pericarditis.

Fever, productive cough and haemoptysis initially pointed towards TB. However, the rapidly worsening renal profile with almost doubling of creatinine on the third day, aggravation of dyspnoea with development of haemoptysis, and rapid deterioration of the liver profile forced us to consider other differentials. Arthralgias, lymphopenia, raised globulins and markedly raised ESR brought our mind towards some autoimmune process, but antinuclear antibody (ANA) and direct Coombs test were negative. His sputum and pleural fluid gene Xpert for TB were negative and later on anti-double stranded DNA(anti-dsDNA) was found to be markedly raised with low complement levels, pointing towards active autoimmune phenomena. Thus presence of arthralgia, effuse-constrictive pericarditis and pleural effusion,

Department of Medicine, Dow University of Health Sciences, Karachi.
Correspondence: Hina Aslam. E-mail: md.hinaaslam@gmail.com

lymphopenia, and high anti-dsDNAtitre supported the diagnosis of SLE according to criteria proposed by the American College of Rheumatology (ACR).[3] He was given a short course of steroids (prednisolone 1mg/kg/day) for SLE and thyroxine 50 microgram per day for hypothyroidism after which there was marked improvement. He was then referred to a specialised cardiology unit for pericardiectomy.

Discussion

Apart from its antiviral properties, IF-alpha has anti-proliferative, anti-angiogenic, anti-tumour and immunomodulatory properties. Immunomodulatory effects of IF may not only aggravate and unmask the pre-existing autoimmune processes, but can even induce de novo autoimmune diseases.[1] The mechanism underlying the development of autoimmune diseases is not completely understood and includes increased expression of major histocompatibility complex (MHC) class I and II antigens, increased conversion of monocytes to antigen presenting dendritic cells, activation of T helper lymphocytes by auto antigens, induction of inflammatory cytokines and direct antibody production and inhibition of suppressor T cells by type I interferon.

Less than 1% of patients treated with IF-alpha develop SLE,[4] an autoimmune disease whose serological hallmark is the development of autoantibodies against nuclear, cytoplasmic and membrane proteins. Patients typically develop high titres of ANA, and anti-dsDNA. ANA is generally used for screening and has a sensitivity of 95% for SLE. In contrast, an anti-dsDNA, having sensitivity of only 70%, is not a good screening test, but due to its high specificity (99.5%) it is rather used as a confirmatory test.[5]

Like other autoimmune diseases, SLE is predominantly a disease of women. Prevalence of SLE in males is much lower than females. More than 90% cases of SLE occur in women, frequently starting at child-bearing age. Overall, 65% patients manifest symptoms between ages 18 and 55 with only 20% manifesting symptoms before 18 years of age.[6]

Dysfunction of thyroid and development of thyroid autoantibodies have been seen in patients with chronic hepatitis both before and after treatment with IF-alpha. Its prevalence is much less frequently seen with hepatitis B, with estimated incidence of only 2-4% compared to hepatitis C, where incidence is estimated to be approximately 20%. Moreover, there is lower incidence of thyroid dysfunction after IF-alpha therapy in chronic hepatitis B and D compared to hepatitis C. Although development of anti-thyroid antibodies without clinical disease occurs in up to 5-40% of patients, but only 5-10% develop clinical thyroid disease.[7]

A few factors made it challenging to diagnose SLE in our case. First of all, our patient was a young male of 16 years, not fitting the typical age and gender of SLE. Secondly, he did not present with typical signs and symptoms of SLE like oral ulcers, photosensitivity or rash. Thirdly and above all, his negative ANA test made it highly challenging to establish the diagnosis until anti-dsDNA was found to be markedly raised with low complement levels, pointing towards active autoimmune phenomena. Moreover, sputum and pleural fluid gene Xpert for TB, which has a sensitivity of 88% and specificity of 98%[8] was negative, thus excluding TB.

Although SLE is generally considered a disease of women, but the incidence in males and females is equal after IF-alpha use as seen with other drug-induced SLEs. Small percentages of patients with clinical manifestations of SLE have ANA negative lupus, first described in 1976.[9] One of the possible explanations of negative ANA test is that the target antigen in cultured cells is inadequately available to bind ANAs present in patient's serum when exposed to it.[10] The patient's serum is incubated with the target antigen and then exposed to fluorescent antibody, which react with antigen-bound ANAs. Thus, in any ANA test, the antigens are critical and it has been seen that negative ANA results are due to substrates with inadequate antigenicity. One entity called Lupus-like syndrome has been described if less than 4 out of 11 ACR criteria are met, many of which had negative ANA. However, our patient met the ACR criteria for SLE (which has a sensitivity of 85% and specificity of 95%[11]) as he had arthralgias, pleural and pericardial effusions, lymphopenia and raised anti-dsDNA, and met 5 out of 11 criteria according to newer Systemic Lupus International Collaboration Clinics Criteria (SLICC criteria) due to decreased complement levels.[12]

Conclusion

SLE should be considered after the use of interferon in both genders and across all ages in patients who test negative for ANA and do not present with typical clinical manifestations of SLE, such as skin rash and arthritis.

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