Pegylated Interferon-alpha induced Autoimmune Hemolytic Anemia in Chronic Hepatitis C A Case Report

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Abstract

A 29-year-old male patient with chronic hepatitis C, treated with interferon-alpha therapy, presented with fatigue and shortness of breath. Autoimmune hemolytic anemia (AIHA) was diagnosed. Other potential etiologies of AIHA were ruled out. An association with interferon-alpha therapy was highly suspected. So, interferon-alpha therapy was discontinued and prednisolone therapy instituted. There was resolution of the hemolytic anemia. Physicians should be aware that interferon alpha can be the cause of AIHA during a combined treatment containing interferon-alpha plus ribavirin for chronic hepatitis C.

Key Words: Hepatitis C, Interferon , Autoimmune hemolytic anemia.

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Introduction

Hepatitis C infection is spread worldwide. We all know that it is common in Taiwan as well. It becomes chronic in about 80% of infected patients. Approximately 20% to 30 % of those chronically infected will develop cirrhosis and a proportion of these will develop hepatocellular carcinoma(1,2). The standard treatment for hepatitis C is interferon-alpha (standard or pegylated) plus ribavirin. This combined treatment has increased the number of sustained virologic responders which is namely the clearance of serum HCV RNA 6 months after therapy withdrawal , but is associated with several adverse effects. Most notably, ribavirin is associated with hemolytic anemia because of its direct toxic effect on red blood cells (3,4). We report a case of interferon-alpha induced auto-immune hemolytic anemia in our patient who initially received combined treatment.

Case report

A 29-year-old Taiwanese male patient presented with two-week history of fatigue, general weakness, pale looking and shortness of breath on walking about 100 meters on level ground. He denied bloody stool or tarry stool in recent days. Past history had chronic hepatitis C infection since one year ago. His molecular analysis of HCV showed genotyping 1a and 4.97 x 106 copies/ml. He had been prescribed ribavarin 1000mg daily and pegylated interferon-alpha-2a 180mcg therapy weekly for 7 doses. Because of low hemoglobin (7.6g/dl) detected at OPD, ribavirin therapy was stopped . But interferon therapy was continued. There was found to have continued pallor and worsening of dyspnea even after cessation of ribavirin therapy. His past history was also significant as he had hypothyroidism for four years and taking thyroxin treatment at other hospital. He denied family history of hematologic diseases. Because of continued worsening of pallor and exertional dyspnea, he was admitted to our hospital for further management.

On admission, his vital signs were within normal limits. Physical examination was significant for having pallor at conjunctivae. Neck had diffuse goiter with smooth surface, soft in consistency and no bruit. No cervical lymph adenopathy was detected. Heart examination showed grade 2/6 soft systolic murmur at left sternal border. Chest examination showed clear breath sound. Abdomen examination showed no palpable hepatosplenomegaly. Extremities had no edema at legs. Laboratory investigations on admission showed Hemoglobin (Hb) 5.5g/dl, Hct 16.2%,MCV 103.8 cu , WBC 5090/c.mm, Platelet 190,000/c.mm, GOT 33U/L, GPT 16U/L, LDH 229 U/L, BUN 11mg/dl, Cr 0.9mg/dl, Reticulocyte 9%, Total Bilirubin 2.5mg/dl, Direct bilirubin 0.4mg/dl, Haptoglobin <29.5mg/dl, C4 6.69mg/dl(10-40mg/dl), C3 73.9mg/dl (90-180mg/dl) , negative Rheumatoid factor (RF), negative Antinuclear antibody (ANA). Stool test showed negative occult blood and no finding of ova & parasite. Upper gastrointestinal endoscopy also showed negative finding. Initial investigations showed macrocytic anemia probably due to acute hemolysis. Later follow up investigations showed AntiHIV- negative, STS-RPR- nonreactive, HbsAg-negative, T3 90ng/dl(90-190ng/dl), Free T4 0.70ng/dl(0.7-1.8ng/dl), TSH 10.96uIU/ml(0.3-6.5uIU/ml), Antithyroglobulin 10.5IU/ml (<115IU/ml), negative

Antimicrosomal antibody , RBC morphology-anisocytosis , positive direct Coomb's test , negative indirect Coomb's test, folic acid >20.00ng/ml(3.0-17.8ng/ml), vitamin B12 611.0pg/ml(200-950pg/ml). Bone marrow examination disclosed normocellular marrow with moderate erythroid hyperplasia. Then we confirmed the autoimmune acute hemolytic anemia in this patient. Then he was prescribed with prednisolone 60mg per day. His hemoglobin level was found to rise gradually after steroid therapy. Follow up hemoglobin levels were 12.8g/dl on 4weeks later, and 14.8g/dl on 7weeks later.

Discussion

Chronic hepatitis C virus (HCV) infection, including its squeal, is an important healthcare problem in Taiwan . The seroprevalence of HCV infection in first-time blood donors in Taiwan is 1.2% and an estimated 2-5% in the general population, with a great geographic variation. Genotype 1b is the most prevalent HCV genotype in Taiwan, with a prevalence rate of 50% to 70% (5). Interferon alpha is effective in the treatment of chronic hepatitis C. The rate of response to interferon is enhanced by increasing the IFN dose. Extending the treatment duration can reduce the relapse rate. Addition of ribavirin to interferon increases the sustained virologic response (SVR) (6). Anemia is extremely common among patients taking pegylated interferon and ribavirin combination therapy for chronic hepatitis C. In a retrospective analysis in 677 patients who were treated with non-pegylated interferon and ribavirin, 56 % experienced a decrease in Hb ≥3 g/dl and in approximately 10% the Hb declined to less than 10 g/dl (7).Standard interferon and ribavirin therapy is associated with mean maximal Hb decreases within the first 12 weeks of 2.9 to 3.1 g/dl (8). In more recent studies of pegylated interferon and ribavirin, the development of anemia and need for dose reductions are similar to those previously reported with standard interferon and interferon. The maximal decrease in Hb is reported at 3.7 g/dl (9) in individuals with normal renal function, with the development of Hb less than 10 g/dl ranging between 9% to 16 % (10,11). Autoimmune hemolytic anemia has been described as a rare complication following the use of interferon for the treatment of viral hepatitis. The etiology of autoimmune hemolytic anemia in this setting is unclear (12,13). But there is proposed that interferon has important immunomodulatory properties, and treatment can induce autoimmune phenomena, the most frequent being autoimmune thyroiditis with either hypothyroidism or hyperthyroidism, especially in predisposed patients (14). Other autoimmune diseases can develop or be exacerbated during interferon therapy, including psoriasis, vitiligo, rheumatoid arthritis, lichen planus, sarcoidosis, dermatitis herpetiformis, and type 1 diabetes mellitus(15-21).This 29-year-old man with HCV presented with severe anemia occurring after 7 weeks of interferon-alpha plus ribavarin therapy for chronic hepatitis C. Ribavarin was initially removed from therapy as soon as hemoglobin level dropped. But interferon-alpha therapy was continued as monotherapy. But we found out that remarkable further decrease of hemoglobin level in this patient is related to autoimmune hemolysis. Several reasons make the role of interferon therapy very likely : (1) the chronology of the anemic event after cessation of ribavirin; (2) anemia related to autoimmune

hemolysis notably by reduced heptoglobin level and positive direct Coomb's test; (3) no other proven events of acute hemorrhage and bone marrow suppression (4) anemia resolved after discontinuation of interferon and institution of steroid therapy. We conclude that if an unexplained drop in hemoglobin occurs with a chronic hepatitis C patient receiving interferon-alpha and ribavirin therapy, not only ribavirin can be a culprit, but also interferon-alpha induced autoimmune mediated hemolysis should be considered.

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長效型干擾素引發之自體免疫溶血性貧血
－病例報告－

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摘　要

長效型干擾素α-2a最常見的血液副作用包括中性白血球減少，貧血及血小板減少，本病例是少見的自體免疫性溶血性貧血。此病患爲29歲男性因患慢性C型肝炎接受長效型干擾素α-2a，每週180mcg，共7劑量，發現貧血症狀，甚至停止Ribavirin，其血紅素仍繼續下降，經証實爲自體免疫性溶血症，以類固醇治療及停止干擾素治療，其血紅素完全恢復。我們結論在使用干擾素合併Ribavirin治療時，發現有貧血現象應考慮Ribavirin引發溶血性貧血外，自體免疫性溶血性貧血也應列入鑑別診斷。

關鍵字：慢性C型肝炎，自體免疫溶血性貧血長效型干擾素

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